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(54) Title: SUBSTITUTED ALKYLDIAMINES

(57) Abstract: The invention relates to novel compounds which are substituted alkyldiamino derivatives of formula (I). The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I) and especially their use as inhibitors of the plasmodium falciparum protease plasmepsin II or related aspartic proteases.

SUBSTITUTED ALKYLDIAMINES

The invention relates to novel compounds which are substituted alkyldiamino derivatives of the general formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of general formula I and especially their use as inhibitors of the plasmodium falciparum protease plasmepsin II or related aspartic proteases.

Background of the invention:

Malaria is one of the most serious and complex health problems affecting humanity in the 21st century. The disease affects about 300 million people worldwide, killing 1 to 1.5 million people every year. Malaria is an infectious disease caused by four species of the protozoan parasite Plasmodium, P. falciparum being the most severe of the four. All attempts to develop vaccines against P. falciparum have failed so far. Therefore, therapies and preventive measures against malaria are confined to drugs. However, resistance to many of the currently available antimalarial drugs is spreading rapidly and new drugs are needed.

P. falciparum enters the human body by way of bites of the female anophelino mosquito. The plasmodium parasite initially populates the liver, and during later stages of the infectious cycle reproduces in red blood cells. During this stage, the parasite degrades hemoglobin and uses the degradation products as nutrients for growth [1]. Hemoglobin degradation is mediated by serine proteases and aspartic proteases. Aspartic proteases have been shown to be indispensable to parasite growth. A non-selective inhibitor of aspartic proteases, Pepstatin, inhibits the growth of P. falciparum in red blood cells in vitro. The same results have been obtained with analogs of pepstatin [2], [3]. These results show that inhibition of parasite aspartic proteases interferes with the life cycle of P. falciparum. Consequently, aspartic proteases are targets for antimalarial drug development.

The present invention relates to the identification of novel low molecular weight, non-peptidic inhibitors of the plasmodium falciparum protease plasmepsin II or other related aspartic proteases to treat and/or prevent malaria.

The compounds of general formula I were tested against plasmepsin II, HIV-protease, human cathepsin D, human cathepsin E and human renin in order to determine their biological activity and their selectivity profile.

In vitro Assays:

The fluorescence resonance energy transfer (FRET) assay for HIV, plasmepsin II, human cathepsin D and human cathepsin E.

The assay conditions were selected according to reports in the literature [4 - 7]. The FRET assay was performed in white polysorp plates (Fluoronunc, cat n° 437842 A). The assay buffer consisted of 50 mM Na acetate pH 5, 12,5% glycerol, 0.1% BSA + 392 mM NaCl (for HIV-protease).
The incubates per well were composed of:

- 160 µl buffer
- 10 µl inhibitor (in DMSO)
- 10 µl of the corresponding substrate in DMSO (see table A) to a final concentration of 1 µM
- 20 µl of enzyme to a final amount of x ng per assay tube (x = 10 ng/assay tube plasmepsin II, x = 100 ng/assay tube HIV-protease, x = 10 ng/assay tube human cathepsin E and x = 20 ng/assay tube human cathepsin D)

The reactions were initiated by addition of the enzyme. The assay was incubated at 37°C for 30 min (for human cathepsin E), 40 min (for plasmepsin II and HIV-protease) or 120 min (for human cathepsin D). The reactions were stopped by adding 10% (v/v) of a 1 M solution of Tris-base. Product-accumulation was monitored by measuring the fluorescence at 460 nm.

Auto-fluorescence of all the test substances is determined in assay buffer in the absence of substrate and enzyme and this value was subtracted from the final signal.

Aspartyl protease	substrate		enzyme concentration ng/at (nM)	Buffer	pH	incubation time minutes
	sequence	substrate concentration µM				
HIV	Dabcyl-Abu-SQNY:PIVN-EDANS	1	100 (22.5)	50 mM Na acetate ; 12,5 % glycerol ; 0.1 % BSA 392 mM NaCl	5	40
Plasmepsin II	Dabcyl-ERNleF:LSFP-EDANS	1	10 (1.25)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	40
h Cathepsin D	Dabcyl-ERNleF:LSFP-EDANS	1	20 (2.5)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	120
h Cathepsin E	Dabcyl-ERNleF:LSFP-EDANS	1	10 (1.25)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	30

Table A: Summary of the conditions used for the aspartyl proteases fluorescent assays. (at = assay tube)

Enzymatic in vitro assay for renin:

The enzymatic in vitro assay was performed in polypropylene plates (Nunc, Cat No 4-42587A). The assay buffer consisted of 100 mM sodium phosphate, pH 7.4, including 0.1% BSA. The incubates were composed of 190 µL per well of an enzyme mix and 10 µL of renin inhibitors in DMSO. The enzyme mix was premixed at 4°C and composed as follows:

- human recombinant renin (0.16 ng/mL)
- synthetic human tetradecapeptide renin substrate (0.5 µM)
- hydroxyquinoline sulfate (0.1 mM)

The mixtures were then incubated at 37°C for 3 h.

To determine the enzymatic activity and its inhibition, the accumulated Angiotensin I was detected by an enzyme immunoassay (EIA). 10 µL of the incubates or standards were transferred to immuno plates which were previously

coated with a covalent complex of Angiotensin I and bovine serum albumin (Ang I – BSA). 190 µL of Angiotensin I-antibodies were added and a primary incubation made at 4°C over night. The plates were washed 3 times and then incubated for one hour at room temperature with a *biotinylated anti-rabbit antibody.* Thereafter, the plates were washed and incubated at room temperature for 30 min with a *streptavidin-peroxidase complex*. After washing the plates, the *peroxidase substrate* ABTS (2.2'-Azino-di-(3-ethyl-benzthiazolinsulfonate), was added and the plates incubated for 10-30 min at room temperature. After stopping the reaction with 0.1 M citric acid pH 4.3 the plate is evaluated in a microplate reader at 405 nm.

Table 1: IC_{50} values (nM) for selected compounds on plasmepsin II:

Example Nr:	IC50 (nM) on plasmepsin II
Example 1	115
Example 21	469
Example 22	858
Example 23	252
Example 25	596
Example 20	846
Example 38	325
Example 51	691
Example 52	834
Example 53	125
Example 54	312
Example 56	659
Example 57	351
Example 58	754
Example 59	380
Example 60	198
Example 61	57
Example 68	714
Example 69	8230

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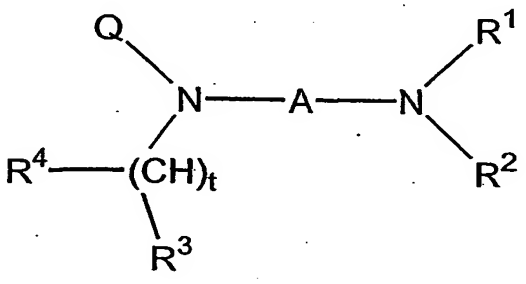
The present invention relates to novel, low molecular weight organic compounds, which are substituted dialkylamines of the **general formula I:**



General Formula I

wherein

Q represents $-SO_2-R^5$; $-CO-R^5$; $-CO-NH-R^5$; $-CO-N(R^5)(R^6)$; $-CO-OR^5$; $-(CH_2)_p-R^5$; $-(CH_2)_p-CH(R^5)(R^6)$;

R^1 and **R^2** represent propyl; butyl; pentyl; hexyl; ω-hydroxy-propyl; ω -hydroxy-butyl; ω-hydroxy-pentyl; ω-hydroxy-hexyl; lower alkoxy-propyl; lower alkoxy-butyl; lower alkoxy-pentyl; lower alkoxy-hexyl; aryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; heterocyclyl; and can be the same or different; or **R^1** and **R^2** and the nitrogen atom together can represent a ring such as azetidin; azepan;

R^3 represents lower alkyl; lower alkenyl; aryl; heteroaryl; cycloalkyl; heterocyclyl; aryl-lower alkyl; heteroaryl-lower alkyl; cycloalkyl-lower alkyl; heterocyclyl-lower alkyl; aryl-lower alkenyl; heteroaryl-lower alkenyl; cycloalkyl-lower alkenyl; heterocyclyl-lower alkenyl;

R^4 represents hydrogen; $-CH_2-OR^7$; $-CO-OR^7$; lower alkyl;

R^5 and **R^6** represent lower alkyl; lower alkenyl; aryl; heteroaryl; cycloalkyl; heterocyclyl; aryl-lower alkyl; heteroaryl-lower alkyl; cycloalkyl-lower alkyl; heterocyclyl-lower alkyl; aryl-lower alkenyl; heteroaryl-lower alkenyl; cycloalkyl-lower alkenyl; heterocyclyl-lower alkenyl;

R^7 represents hydrogen, lower alkyl; cycloalkyl; aryl; cycloalkyl-lower alkyl; aryl-lower alkyl;

t represents the whole numbers 0 (zero) or 1 and in case t represents the whole number 0 (zero), **R^4** is absent;

p represents the whole numbers 0 (zero), 1 or 2;

A represents $-(CH_2)_n-$;

n represents the whole numbers 2, 3, 4 or 5;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

In the definitions of the **general formula I** – if not otherwise stated – the expression lower means straight and branched chain groups with one to seven carbon atoms, preferably 1 to 4 carbon atoms. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec.-butyl, tert.-butyl, pentyl, hexyl, heptyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-butoxy, sec.-butoxy and tert.-butoxy etc. Lower alkylendioxy-groups as substituents of aromatic rings onto two adjacent carbon atoms are preferably methylene-dioxy and ethylene-dioxy. Lower alkylen-oxy groups as substituents of aromatic rings onto two adjacent carbon atoms are preferably ethylen-oxy and propylen-oxy. Examples of lower alkanoyl-groups are acetyl, propanoyl and butanoyl. Lower alkenylen means e.g. vinylen, propenylen and butenylen.

The expression **cycloalkyl**, alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 6 carbon atoms , e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl which may be substituted with lower alkyl groups.

The expression **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings may be substituted with lower alkyl, lower alkenyl, aryl; examples of such rings are morpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl etc. and substituted derivatives of such type rings with substituents as outlined hereinbefore.

The expression **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzo-fused five-membred aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five membered aromatic rings containing one oxygen and one nitrogen atom and benzo fused derivatives thereof; five membred aromatic rings containing a sulfur and nitrogen or oxygen atom and benzo fused derivatives thereof; five membered aromatic rings containing three nitrogen atoms and benzo fused derivatives thereof or the tetrazolyl ring; examples of such rings are furanyl, thienyl, pyrrolyl, pyridinyl, indolyl, quinolinyl, isoquinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, imidazolyl, triazinyl, thiazinyl, pyridazinyl, oxazolyl, and the like, whereby such ring systems may be mono-, di- or tri-substituted with aryl; aryloxy, aryl-lower alkoxy, lower alkyl; lower alkenyl; lower alkyl-carbonyl; amino; lower alkyl-amino; bis-(lower-alkyl)-amino; lower alkanoyl-amino; lower alkyl-sulfonamido; aryl-sulfonamido, heteroaryl-sulfonamido; lower alkyl-sulfono; aryl-sulfono; ω-amino-lower alkyl; halogen; hydroxy; carboxyl; lower alkoxy; vinyloxy; allyloxy; ω-hydroxy-lower alkyl; nitro; cyano; amidino; trifluoromethyl; lower alkyl-sulfonyl.

The expression **aryl**, alone or in combination, means six membered aromatic rings and condensed systems like naphthyl or indenyl, whereby such ring systems may be mono-, di- or tri-substituted with aryl, aryloxy, aryl-lower alkyloxy, lower alkyl, lower alkenylen, lower alkyl-carbonyl, aryl-carbonyl, amino, lower alkyl-amino, aryl-amino, bis-(lower-alkyl)-amino, lower alkanoyl-amino, lower alkyl-sulfonamido, aryl-sulfonamido, heteroaryl-sulfonamido, lower alkyl-sulfono, aryl-sulfono, ω-amino-lower alkyl, halogen, hydroxy, carboxyl, lower alkoxy, vinyloxy, allyloxy, ω-hydroxy-lower alkyl, ω-hydroxy-lower alkoxy, nitro, cyano, amidino, trifluoromethyl, lower alkyl-sulfonyl. In the case where the substituent on the aryl unit is another aryl unit, this second aryl unit may again be mono-, di- or tri-substituted with the substituents given as examples above.

It is understood that the substituents outlined relative to the expressions cycloalkyl, heterocyclyl, heteroaryl and aryl have been omitted in the definitions of the general formulae I to VI and in claims 1 to 6 for clarity reasons but the definitions in formulae I to VI and in claims 1 to 6 should be read as if they are included therein.

The expression pharmaceutically acceptable salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid; sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, methylsulfonic acid, p- toluolsulfonic acid and the like or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide.

The compounds of the general formula I can contain one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates and mixtures of diastereomeric racemates.
The present invention encompasses all these forms. Mixtures may be separated in a manner known per se, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

The compounds of the general formula I and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical compositions. They may especially be used to in prevention or treatment of malaria. These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like sprays or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intraveneous form, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula I as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients which are usual in the pharmaceutical industry like lactose, maize or derivatives thereof, talcum, stearinic acid or salts of these materials.

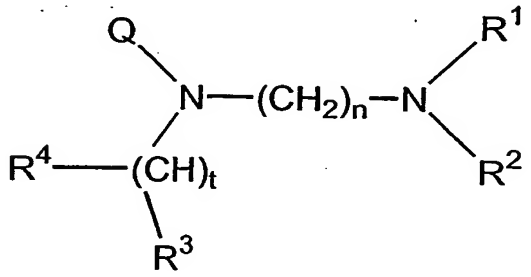
For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols may be used. For the preparation of solutions and sirups e.g. water, polyols saccharose, glucose and related materials are used. Injectables are prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes and the like. Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols.

The compositions may contain in addition preservatives, stability improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti-oxidants and related materials.

The compounds of formula I may also be used in combination with one or more other therapeutically useful substances e. g. with other antimalarials like quinolines (quinine, chloroquine, amodiaquine, mefloquine, primaquine, tafenoquine), peroxide antimalarials (artemisinin derivatives), pyrimethamine-sulfadoxine antimalarials (e.g. Fansidar), hydroxynaphtoquinones (e.g. atovaquone), acroline-type antimalarials (e. g. pyronaridine) and the like.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given in oral form should daily be between about 3 mg and about 3 g, peferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses per day which are of equal weight. As usual, children should receive lower doses which are adapted to body weight and age.

Preferred compounds are compounds of the **formula II**



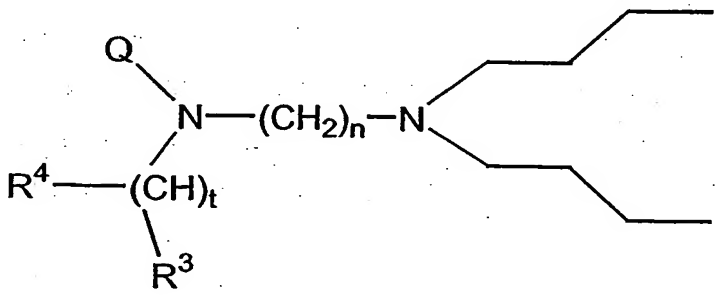
Formula II

wherein

Q, t, R^3 and **R^4** are as defined in general formula I above, **R^1** and **R^2** represent lower alkyl and **n** represents the whole numbers 2 or 3

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

Also preferred compounds are compounds of **formula III**



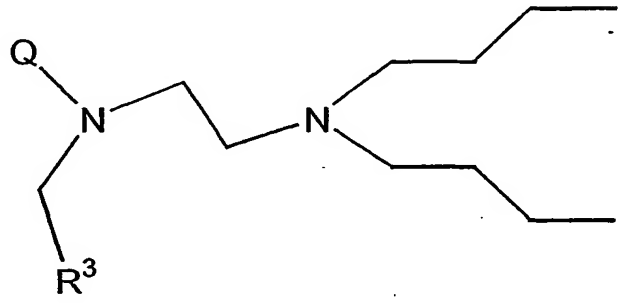
Formula III

wherein

Q, t, R^3 and **R^4** are as defined in general formula I above and **n** represents the whole numbers 2 or 3

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

Especially preferred are also compounds of the **formula IV**



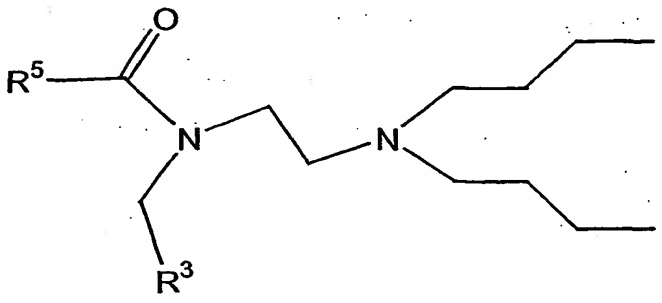
Formula IV

wherein

Q and R^3 are as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

Especially preferred are also compounds of the **formula V**

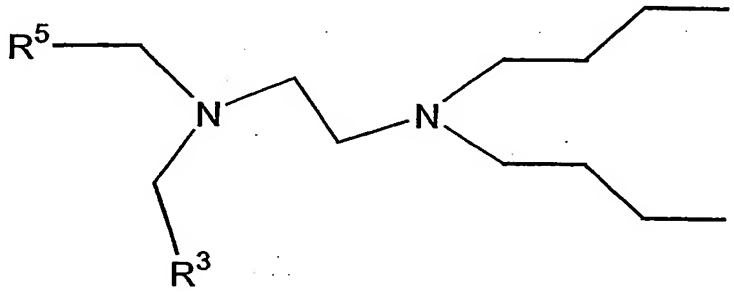


Formula V

wherein R^3 and R^5 are as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

Especially preferred are compounds of the **formula VI**



Formula VI

wherein R^3 and R^5 are as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

Preferred compounds are:

N-(4-Benzyloxybenzyl)-N-(2-dibutylamino-ethyl)-4-pentylbenzamide;

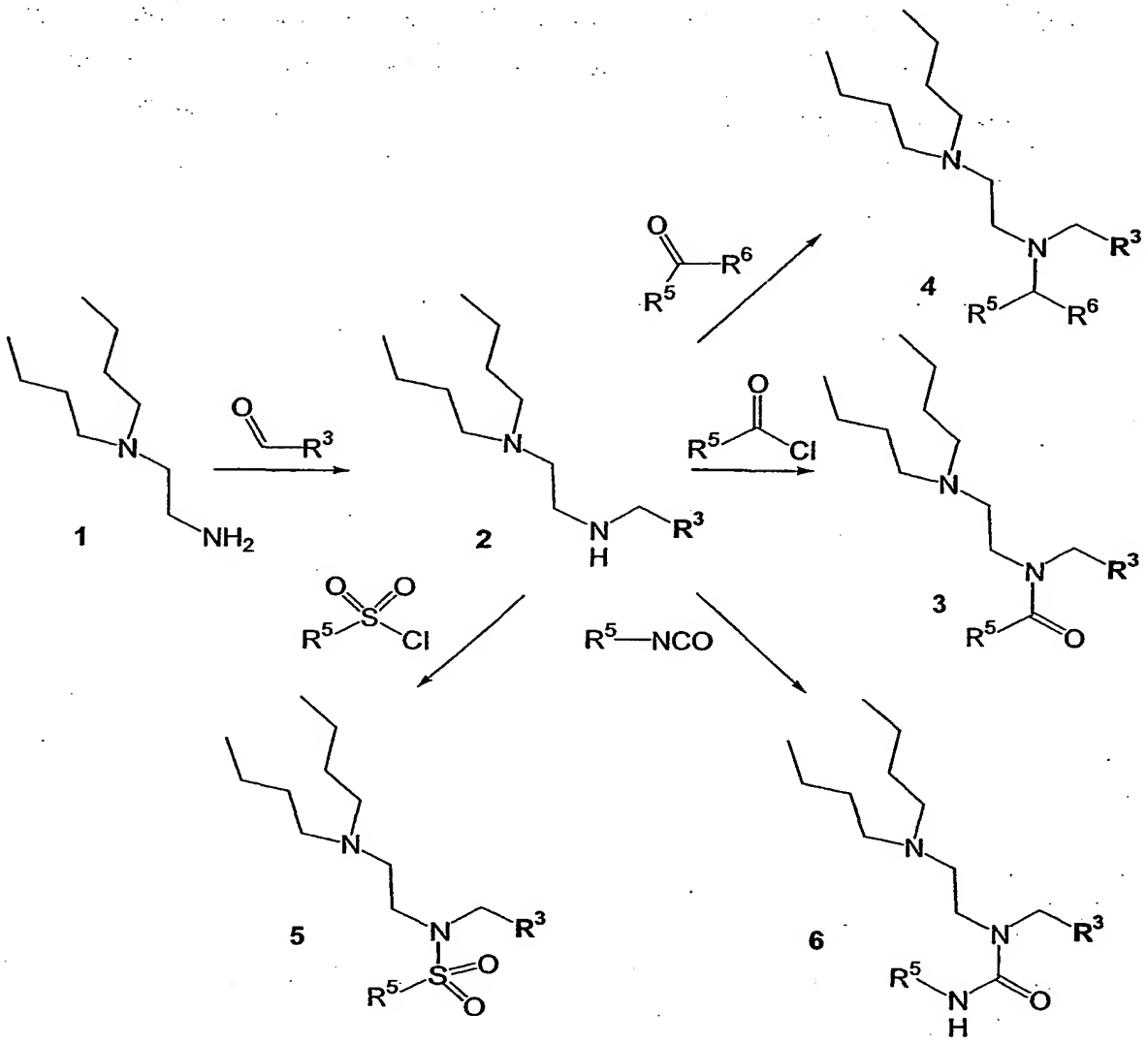
N-Biphenyl-4-ylmethyl-N-(2-dibutylamino-ethyl)-4-pentylbenzamide;

N-(2-Dibutylaminoethyl)-N-[4'-(2-hydroxy-ethoxy)-biphenyl-4-ylmethyl]-4-pentylbenzamide;

N-(4-Benzo[1,3]dioxol-5-yl-benzyl)-N-(2-dibutyl-aminoethyl)-4-pentylbenzamide.

The compounds of the **general formula I** of the present invention may be prepared according to the general sequences of reactions outlined below, wherein R^3, R^4, R^5, R^6, R^7, Q, A, t, n and p are as defined in general formula I above (for simplicity and clarity reasons, only parts of the synthetic possibilities which lead to compounds of formulae I to VI are described). For general methods of certain steps see also pages 16 – 18 and 20 - 21.

Scheme 1: Preparation of substituted N,N-di-n-butylethylenediamines:



Typical procedure for the first reductive amination (synthesis of compound 2):

The amine (**1**) and the aldehyde {R^3-CHO} (1.5 eq.) are mixed in anhydrous methanol and stirred for 6 h. The mixture is treated with sodium borohydride (1.5 eq.) and stirred for 2 h. Purified Amberlyst 15 or another suitable scavenger is added and the suspension is shaken for 12 h. The resin is separated by filtration and washed with methanol. The secondary amine **2** is removed from the resin by adding a 2M methanolic ammonia solution. After 30 min of shaking, the resin is

filtered and washed with methanol. The filtrate is evaporated to yield the pure secondary amine **2**.

If not comercially available, aryl- or heteroaryl substituted benzaldehydes can be prepared as follows:
The aldehyde {R^3-CHO} may be obtained from commercially available formylbenzeneboronic acids and substituted bromo aryls or bromo heteroaryls *via* a Suzuki coupling as described in the literature or as described in the typical procedure D) below.

*Typical procedure for the acylation (synthesis of compound **3**):*

To a solution of the amine **2** in anhydrous ethyl acetate is added vacuum dried Amberlyst 21 or another suitable scavenger, followed by the addition of the carboxylic acid chloride {R^5-(CO)-Cl} (1.5 eq.). After shaking the suspension for 2 hours, an aliquot water is added in order to hydrolyze the excess of carboxylic acid chloride and shaking is continued for 1h. The resin is then removed by filtration, washed with ethyl acetate and the solution is evaporated to yield the pure amide **3**.

The carboxylic acid chlorides {R^5-(CO)-Cl} may be obtained *in situ* from the corresponding carboxylic acid as described in the literature (i. e.: Devos, A.; Rémion, J.; Frisque-Hesbain, A.-M.; Colens,A.; Ghosez, L., *J. Chem. Soc., Chem. Commun.* **1979**, 1180).

The synthesis of the sulfonamide derivatives **5** from the amine **2** is performed in analogy to the above-described procedure.

The urea derivatives **6** are obtained by reaction of the amines **2** in dichloromethane with one equivalent of an isocyanate.

Typical procedure for the second reductive amination (synthesis of compound 4):

The amine (**1**) and the ketone or aldehyde {R^5R^6CO} (1.5 eq.) are mixed in anhydrous dichloromethane and sodium triacetoxyborohydride (1.3 eq.) is added. After stirring the solution for 48 h, methanol is added and the reaction mixture is treated in the same manner as described for the amines **2**.

Compounds of **formula II**, where R^1 and R^2 represent lower alkyl and **n** represents the whole number 2 or 3 are synthesized as described in *scheme 1*.

All chemical transformations can be performed according to well known standard methodologies as described in the literature or as described in the typical procedures above.

The following examples illustrate the invention but do not limit the scop thereof. All temperatures are stated in °C.

List of abbreviations:

Boc or boc	tert.-butyloxycarbonyl
Cbz	benzyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene(1,5-5)
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

General Procedures and Examples:

The following compounds are prepared according to the procedures described for the synthesis of compounds encompassed by the general formulae hereinbefore. All compounds are caracterized by ^{1}H-NMR (300 MHz) and occasionnally by ^{13}C-NMR (75 MHz) (Varian Oxford, 300 MHz; chemical shifts are given in ppm relative to the solvent used; multiplicities: s=singlet, d=doublet, t=triplet, m=multiplet), by LC-MS (Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT; column: 2x30 mm, Gromsil ODS4, 3 µM 120A; gradient: 0-100% acetonitrile in water, 6 min, with 0.05% formic acid, flow: 0.45 ml/min; t_r is given in minutes), by TLC (TLC-plates from Merck, silica gel 60 F_{254}) and occasionally by melting point.

a) General Procedures:

Typical procedure A) for the first reductive amination:

The amine and the aldehyde (1.5 eq.) (which are used as starting materials, are known compounds or the synthesis (in case of the aldehydes) is described below in section c) in Referential Examples 1 to 6) are mixed in anhydrous methanol and stirred for 6 h. The mixture is then treated with sodium borohydride (1.5 eq.) and stirred for 2 h. Purified Amberlyst 15 or another suitable scavenger is added and the suspension is shaken for 12 h. The resin is then separated by filtration and washed with methanol. The secondary amine is removed from the resin by adding a 2M methanolic ammonia solution. After 30 min of shaking, the resin is filtered off and washed with methanol. The filtrate is evaporated to yield the pure secondary amine.

Typical procedure B) for the acylation:

To a solution of the amine in anhydrous ethyl acetate is added vacuum dried Amberlyst 21 or another suitable scavenger, followed by the addition of the carboxylic acid chloride (1.5 eq.) (which either are commercially available or

prepared *in situ* from the corresponding carboxylic acids according to the literature). After shaking the suspension for 2 h, an aliquot of water is added in order to hydrolyze the excess of carboxylic acid chloride and shaking is continued for 1 h. The resin is then removed by filtration, washed with ethyl acetate and the solution is evaporated to yield the pure amide.

Typical procedure C) for the second reductive amination:

The amine and the aldehyde or the ketone (1.5 eq.) are mixed in anhydrous dichloromethane and sodium triacetoxyborohydride (1.3 eq.) is added. After stirring of the solution for 48 h, methanol is added and the reaction mixture is treated in the same manner as described in procedure A).

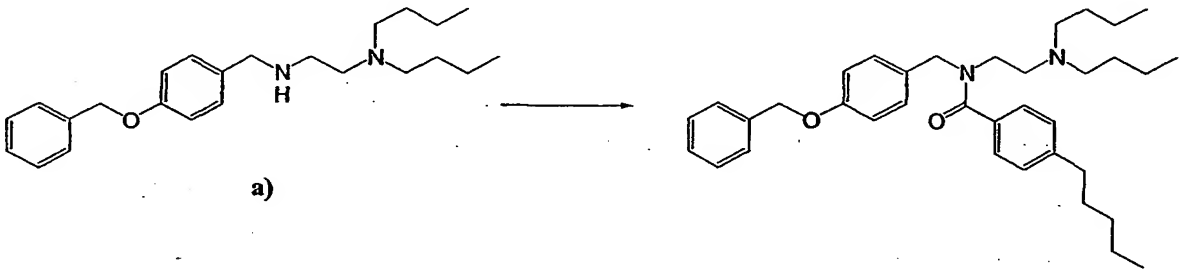
Typical procedure D) for the Suzuki coupling:

To a solution of the bromide in toluene, the boronic acid (1.1 eq.) dissolved in isopropanol is added followed by a 2M aqueous solution of potassium carbonate (5 eq.). The mixture is purged with nitrogen for 10 min and tetrakis(triphenylphosphine) palladium (0.03 eq.) is added. After heating under reflux for 6 h, water is added to the cooled reaction mixture and the product is extracted with ethyl acetate. The organic phase is washed with brine and dried over sodium sulfate. The solvent is evaporated to give the crude aldehyde, which is purified by flash chromatography (ethyl acetate/heptane gradient).

b) Examples:

Example 1:

According to typical procedure B), the secondary amine **a)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



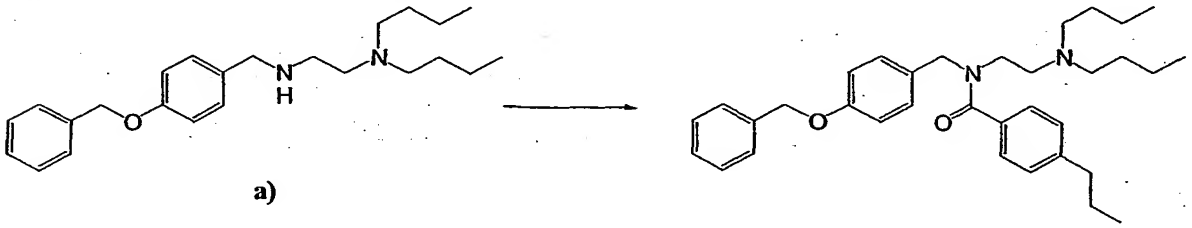
a)

N-(4-Benzyloxybenzyl)-*N*-(2-dibutylamino-ethyl)-4-pentylbenzamide

t_R = 5.39; $(M+H)^+$ = 543.4

Example 2:

According to typical procedure B), the secondary amine **a)**, obtained via typical procedure A), is reacted with 4-n-propylbenzoyl chloride to give



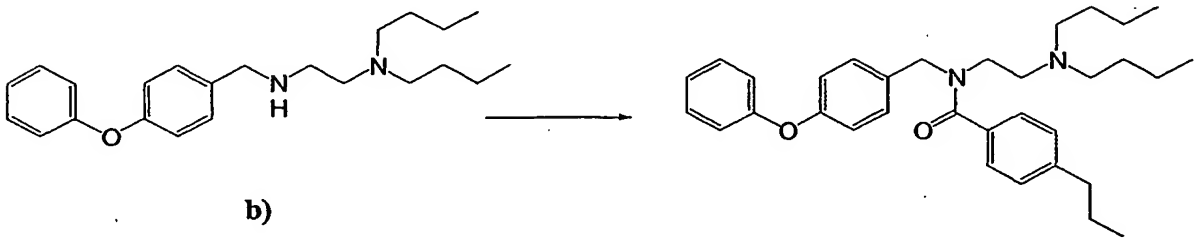
a)

N-(4-Benzyloxybenzyl)-*N*-(2-dibutylamino-ethyl)-4-propylbenzamide

t_R = 4.78; $(M+H)^+$ = 515.49

Example 3:

According to typical procedure B), the secondary amine **b)**, obtained via typical procedure A), is reacted with 4-n-propylbenzoyl chloride to give



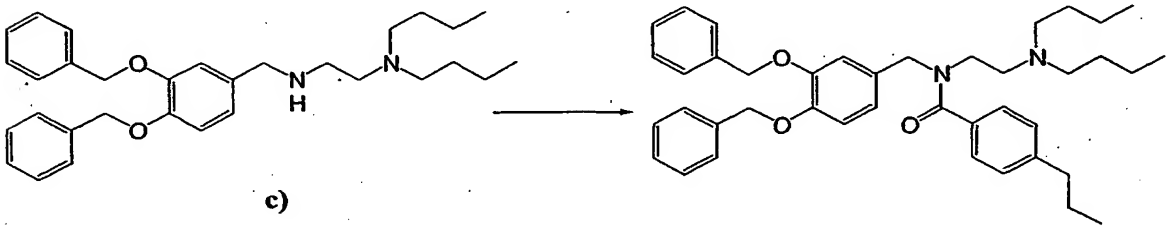
b)

N-(2-Dibutylaminoethyl)-*N*-(4-phenoxy-benzyl)-4-propylbenzamide

t_R = 4.81; $(M+H)^+$ = 501.54

Example 4:

According to typical procedure B), the secondary amine **c)**, obtained via typical procedure A), is reacted with 4-n-propylbenzoyl chloride to give



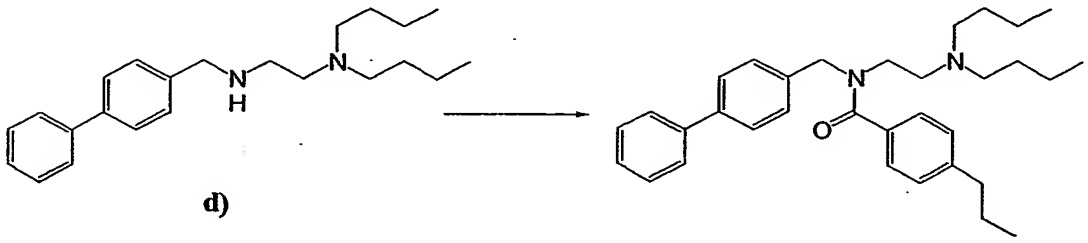
c)

N-(3,4-Bis-benzyloxybenzyl)-*N*-(2-dibutyl-aminoethyl)-4-propylbenzamide

t_R = 5.10; $(M+H)^+$ = 621.62

Example 5:

According to typical procedure B), the secondary amine **d)**, obtained via typical procedure A), is reacted with 4-n-propylbenzoyl chloride to give



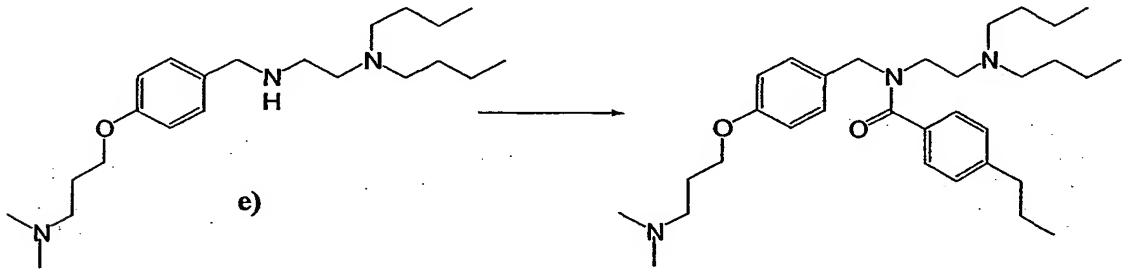
d)

N-Biphenyl-4-ylmethyl-*N*-(2-dibutyl-aminoethyl)-4-propylbenzamide

t_R = 4.78; $(M+H)^+$ = 485.71

Example 6:

According to typical procedure B), the secondary amine **e)**, obtained via typical procedure A), is reacted with 4-n-propylbenzoyl chloride to give



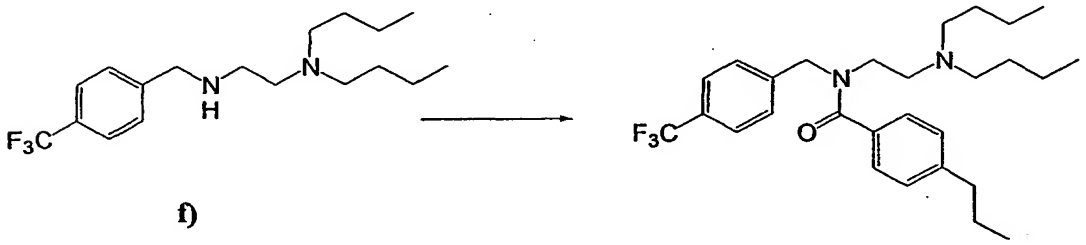
e)

N-(2-Dibutylaminoethyl)-*N*-[4-(3-dimethylamino-propoxy)benzyl]-4-propylbenzamide

t_R = 3.17; $(M+H)^+$ =510.53

Example 7:

According to typical procedure B), the secondary amine **f)**, obtained via typical procedure A), is reacted with 4-n-propylbenzoyl chloride to give



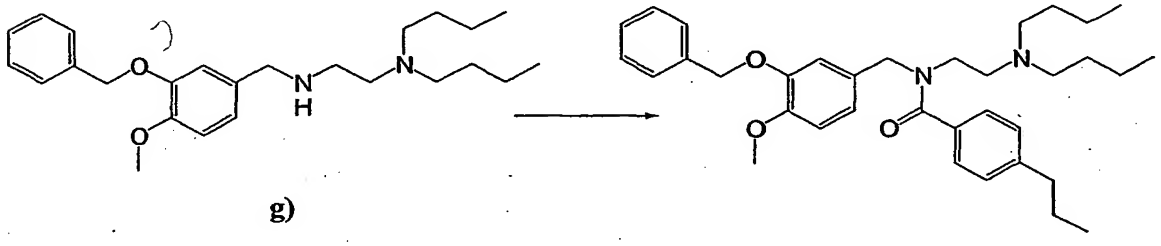
f)

N-(2-Dibutylaminoethyl)-4-propyl-*N*-(4-trifluoromethylbenzyl) benzamide

t_R = 4.58; $(M+H)^+$ =477.56

Example 8:

According to typical procedure B), the secondary amine **g)**, obtained via typical procedure A), is reacted with 4-n-propylbenzoyl chloride to give



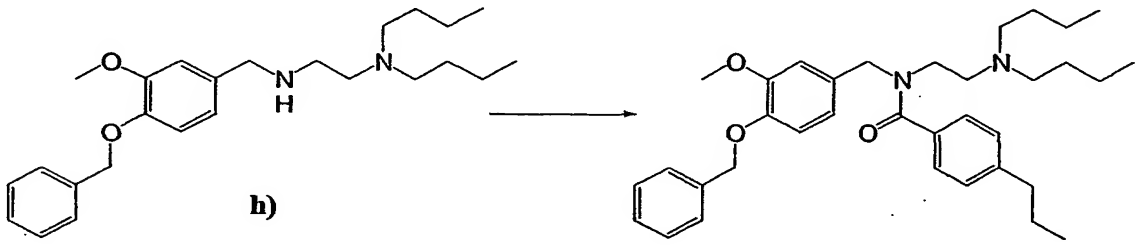
g)

N-(3-Benzyloxy-4-methoxybenzyl)-*N*-(2-dibutylaminoethyl)-4-propylbenzamide

t_R = 4.63; $(M+H)^+$ = 545.60

Example 9:

According to typical procedure B), the secondary amine **h)**, obtained via typical procedure A), is reacted with 4-n-propylbenzoyl chloride to give



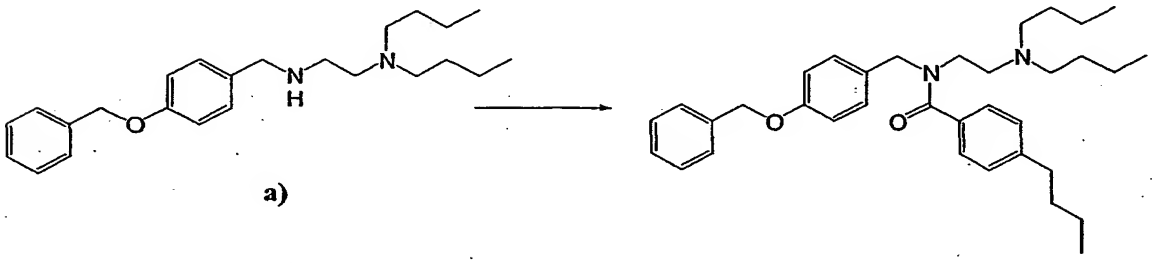
h)

N-(4-Benzyloxy-3-methoxybenzyl)-*N*-(2-dibutylaminoethyl)-4-propylbenzamide

t_R = 4.72; $(M+H)^+$ = 545.55

Example 10:

According to typical procedure B), the secondary amine **a)**, obtained via typical procedure A), is reacted with 4-n-butylbenzoyl chloride to give



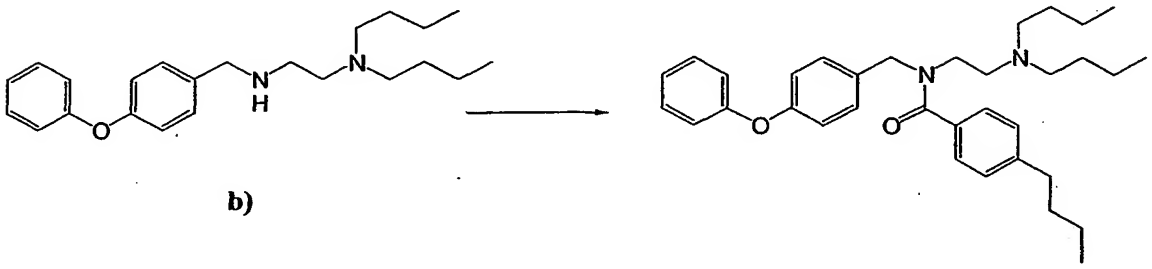
a)

N-(4-Benzyloxybenzyl)-4-butyl-*N*-(2-dibutylaminoethyl) benzamide

t_R = 5.02; $(M+H)^+$ = 529.59

Example 11:

According to typical procedure B), the secondary amine **b)**, obtained via typical procedure A), is reacted with 4-n-butylbenzoyl chloride to give



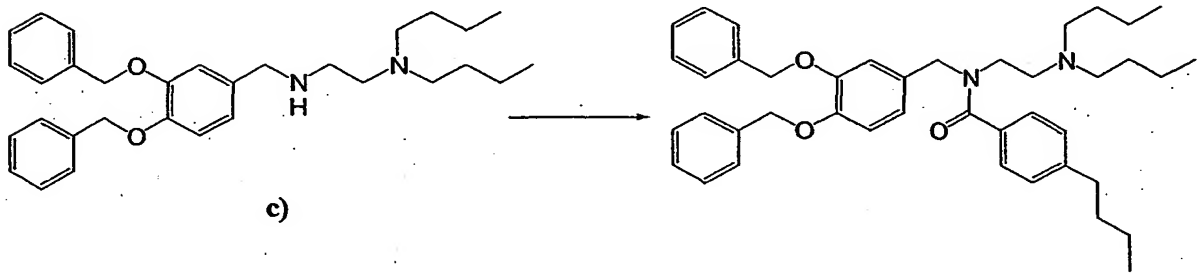
b)

4-Butyl-*N*-(2-dibutylaminoethyl)-*N*-(4-phenoxybenzyl) benzamide

t_R = 4.98; $(M+H)^+$ = 515.55

Example 12:

According to typical procedure B), the secondary amine **c)**, obtained via typical procedure A), is reacted with 4-n-butylbenzoyl chloride to give



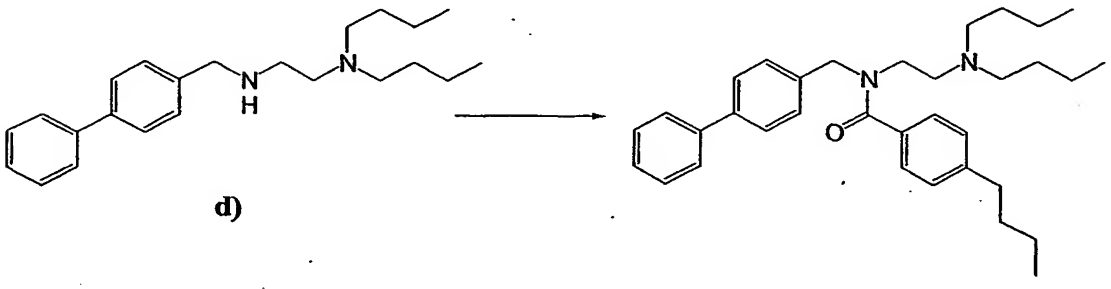
c)

N-(3,4-Bis-benzyloxybenzyl)-4-butyl-*N*-(2-dibutylaminoethyl) benzamide

t_R = 5.26; $(M+H)^+$ =635.55

Example 13:

According to typical procedure B), the secondary amine **d)**, obtained via typical procedure A), is reacted with 4-n-butylbenzoyl chloride to give



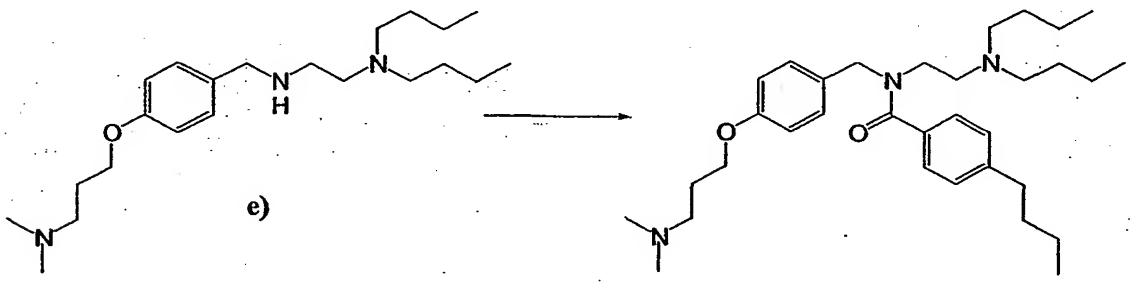
d)

N-Biphenyl-4-ylmethyl-4-butyl-*N*-(2-dibutylaminoethyl) benzamide

t_R = 4.98; $(M+H)^+$ =499.53

Example 14:

According to typical procedure B), the secondary amine **e)**, obtained via typical procedure A), is reacted with 4-n-butylbenzoyl chloride to give



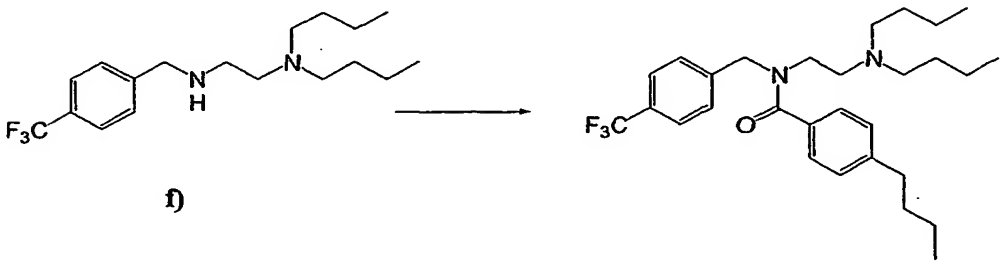
e)

4-Butyl-*N*-(2-dibutylaminoethyl)-*N*-[4-(3-dimethylaminopropoxy)benzyl] benzamide

t_R = 3.41; $(M+H)^+$ = 524.59

Example 15:

According to typical procedure B), the secondary amine **f)**, obtained via typical procedure A), is reacted with 4-n-butylbenzoyl chloride to give



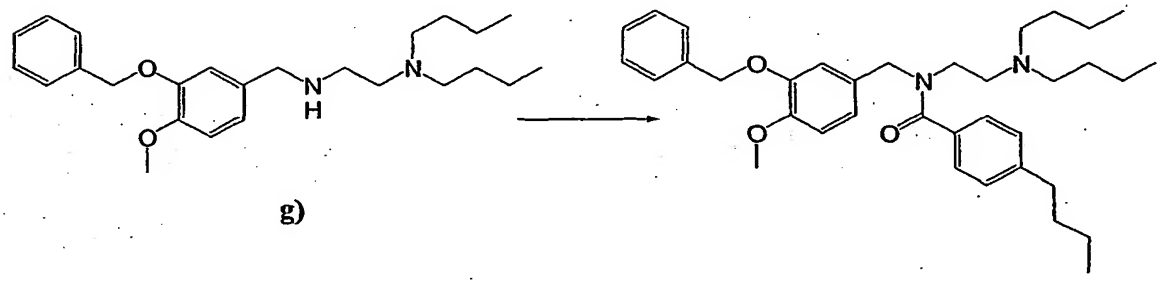
f)

4-Butyl-*N*-(2-dibutylaminoethyl)-*N*-(4-trifluoromethylbenzyl) benzamide

t_R = 4.78; $(M+H)^+$ = 491.50

Example 16:

According to typical procedure B), the secondary amine **g)**, obtained via typical procedure A), is reacted with 4-n-butylbenzoyl chloride to give



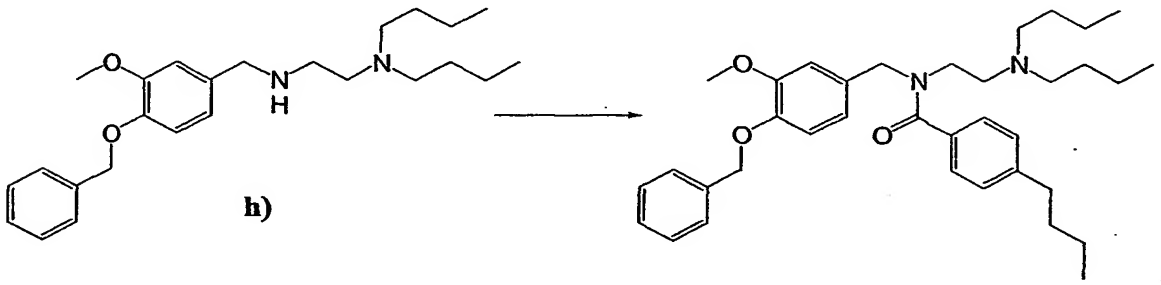
g)

N-(3-Benzyloxy-4-methoxybenzyl)-4-butyl-*N*-(2-dibutylaminoethyl) benzamide

t_R = 4.82; $(M+H)^+$ = 559.58

Example 17:

According to typical procedure B), the secondary amine **g)**, obtained via typical procedure A), is reacted with 4-n-butylbenzoyl chloride to give



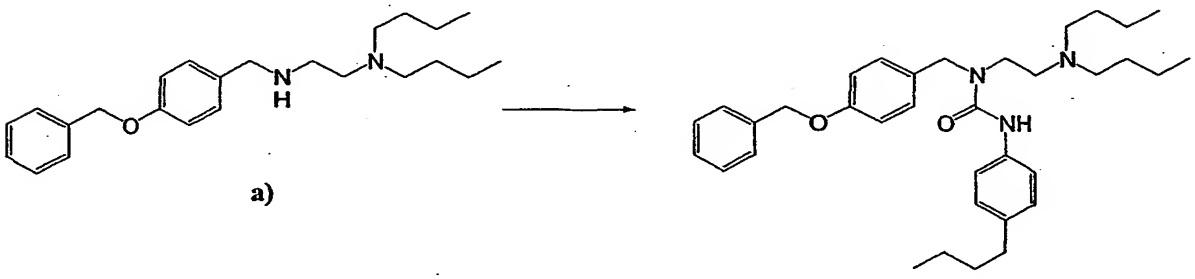
h)

N-(4-Benzyloxy-3-methoxybenzyl)-4-butyl-*N*-(2-dibutylaminoethyl) benzamide

t_R = 4.92; $(M+H)^+$ = 559.50

Example 18:

According to typical procedure B), the secondary amine **a)**, obtained via typical procedure A), is reacted with 4-n-butylphenylisocyanate to give



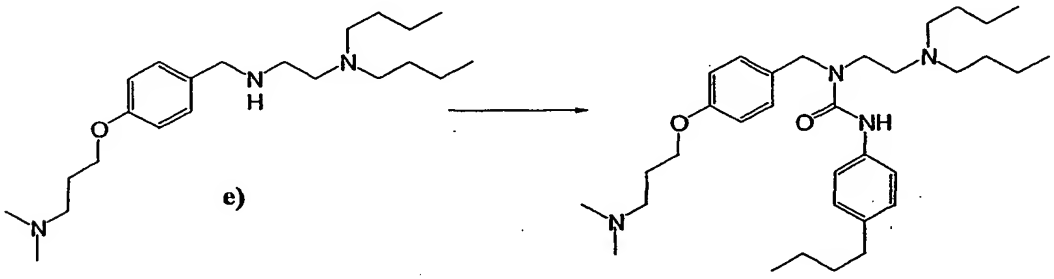
a)

1-(4-Benzyloxybenzyl)-3-(4-butylphenyl)-1-(2-dibutylaminoethyl) urea

t_R = 3.16; $(M+H)^+$ = 544.55

Example 19:

According to typical procedure B), the secondary amine **e)**, obtained via typical procedure A), is reacted with4-n-butylphenylisocyanate to give



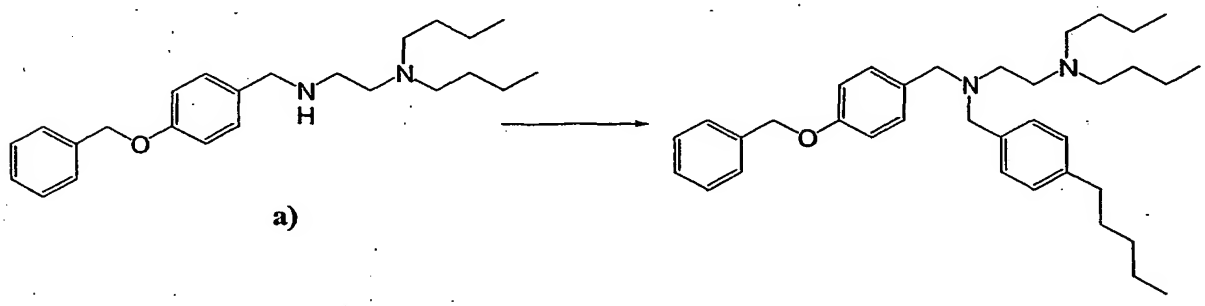
e)

3-(4-Butylphenyl)-1-(2-dibutylaminoethyl)-1-[4-(3-dimethylaminopropoxy)benzyl] urea

t_R = 3.75; $(M+H)^+$ = 539.58

Example 20:

According to typical procedure C), the secondary amine **a)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzaldehyde to give



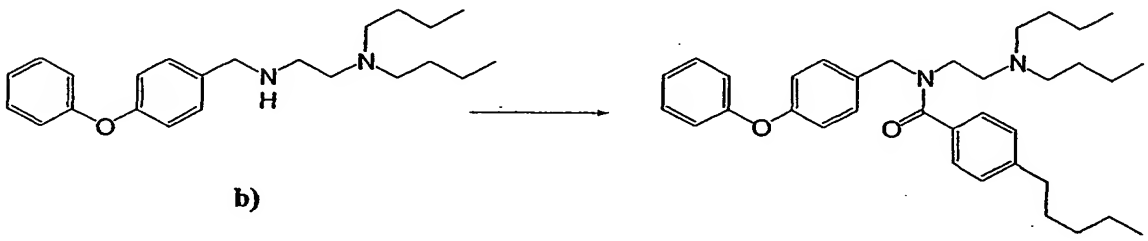
a)

N-(4-Benzyloxybenzyl)-*N'*,*N'*-dibutyl-*N*-(4-pentylbenzyl)ethane-1,2-diamine

t_R = 5.16; $(M+H)^+$ = 529.6

Example 21

According to typical procedure B), the secondary amine **b)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



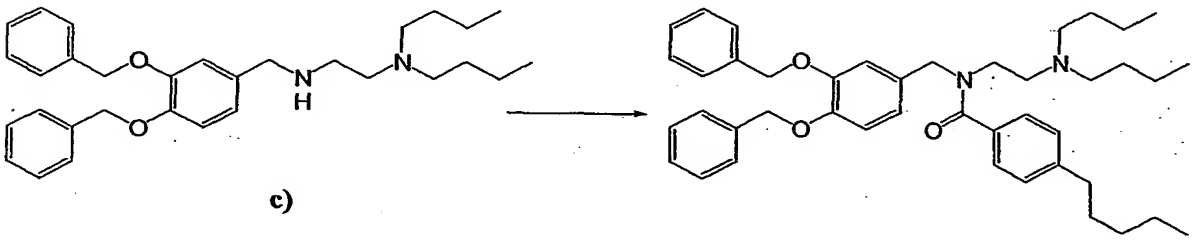
b)

N-(2-Dibutylaminoethyl)-4-pentyl-*N*-(4-phenoxybenzyl) benzamide

t_R = 5.14; $(M+H)^+$ = 529.55

Example 22:

According to typical procedure B), the secondary amine **c)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



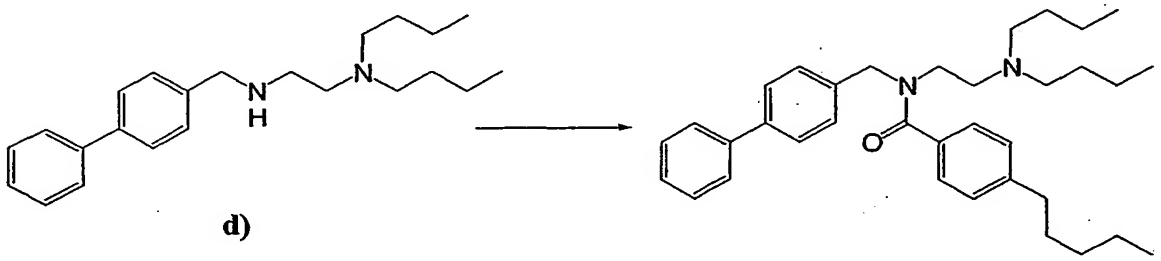
c)

N-(3,4-Bis-benzyloxybenzyl)-*N*-(2-dibutylaminoethyl)-4-pentylbenzamide

t_R = 5.43; $(M+H)^+$ = 650.15

Example 23:

According to typical procedure B), the secondary amine **d)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



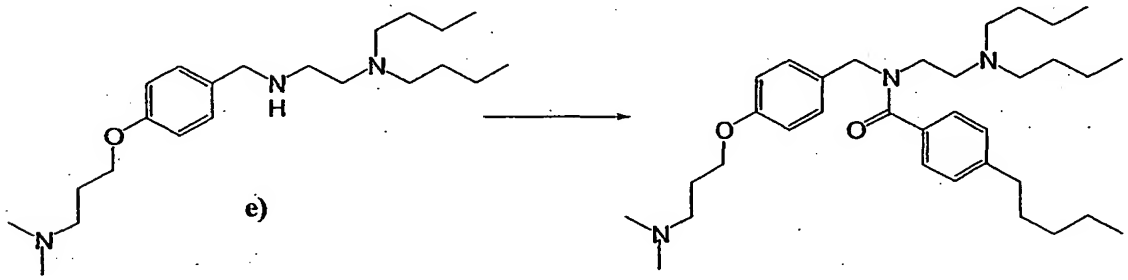
d)

N-Biphenyl-4-ylmethyl-*N*-(2-dibutylamino -ethyl)-4-pentylbenzamide

t_R = 5.10; $(M+H)^+$ = 513.54

Example 24:

According to typical procedure B), the secondary amine **e)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



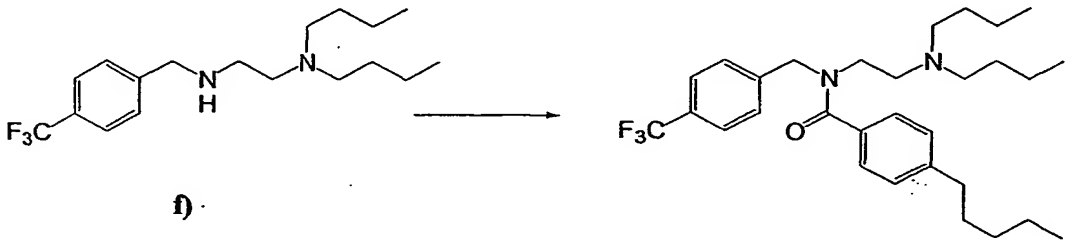
e)

N-(2-Dibutylaminoethyl)-*N*-[4-(3-dimethylamino -propoxy) benzyl]-4-pentylbenzamide

t_R = 3.57; $(M+H)^+$ =538.61

Example 25:

According to typical procedure B), the secondary amine **f)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



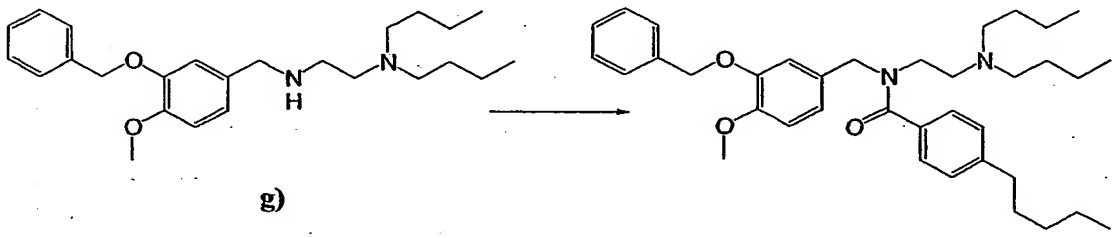
f)

N-(2-Dibutylaminoethyl)-4-pentyl-*N*-(4-trifluoromethylbenzyl) benzamide

t_R = 5.10; $(M+H)^+$ = 505.66

Example 26:

According to typical procedure B), the secondary amine **g)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



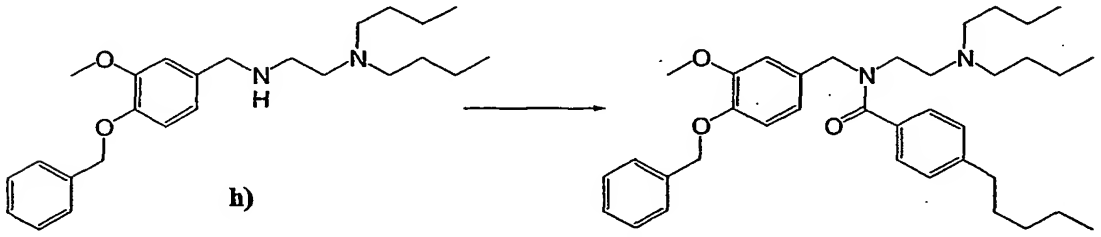
g)

N-(3-Benzyloxy-4-methoxybenzyl)-*N*-(2-dibutylaminoethyl)-4-pentylbenzamide

t_R = 4.98; $(M+H)^+$ = 573.64

Example 27:

According to typical procedure B), the secondary amine **h)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



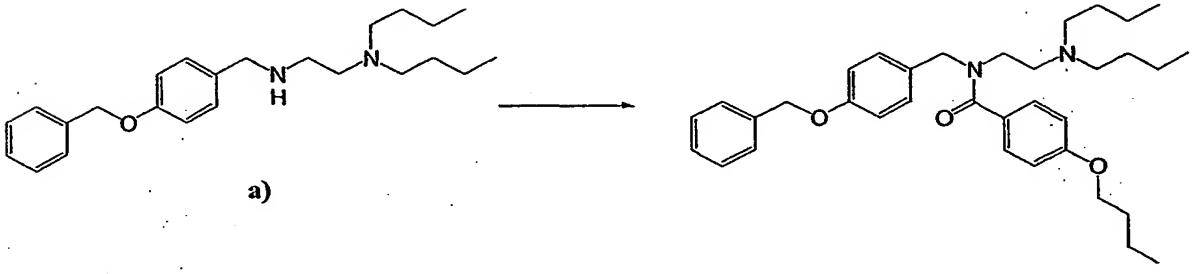
h)

N-(4-Benzyloxy-3-methoxybenzyl)-*N*-(2-dibutylaminoethyl)-4-pentylbenzamide

t_R = 5.07; $(M+H)^+$ = 573.59

Example 28:

According to typical procedure B), the secondary amine **a)**, obtained via typical procedure A), is reacted with 4-n-butoxybenzoyl chloride to give



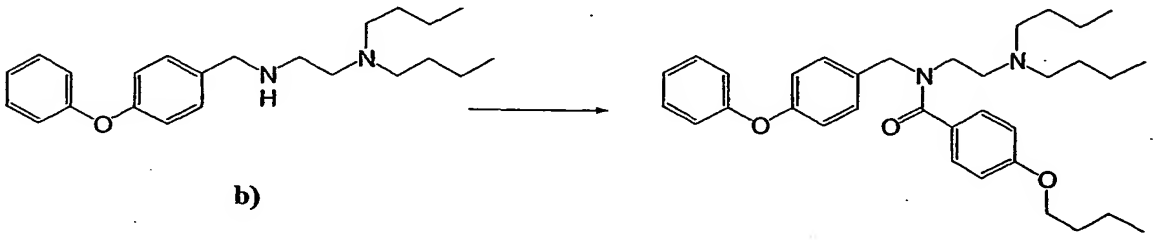
a)

N-(4-Benzyloxybenzyl)-4-butoxy-*N*-(2-dibutylaminoethyl) benzamide

t_R = 4.94; $(M+H)^+$ = 545.54

Example 29:

According to typical procedure B), the secondary amine **b)**, obtained via typical procedure A), is reacted with 4-n-butoxybenzoyl chloride to give



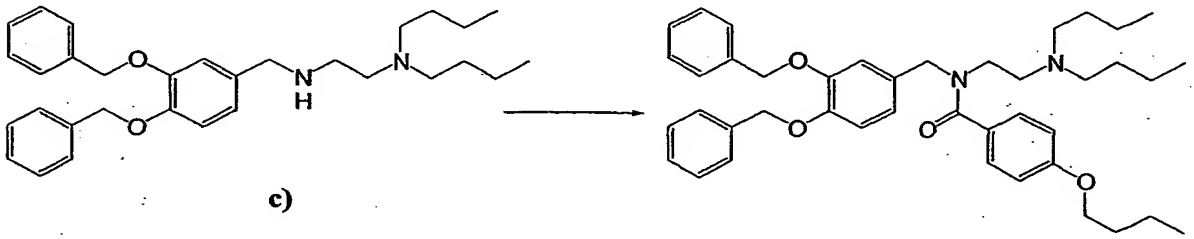
b)

4-Butoxy-*N*-(2-dibutylaminoethyl)-*N*-(4-phenoxybenzyl) benzamide

t_R = 4.93; $(M+H)^+$ = 531.52

Example 30:

According to typical procedure B), the secondary amine **c)**, obtained via typical procedure A), is reacted with 4-n-butoxybenzoyl chloride to give



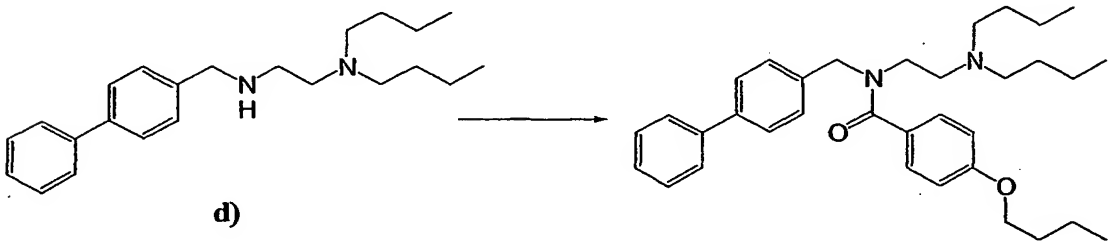
c)

N-(3,4-Bis-benzyloxybenzyl)-4-butoxy-*N*-(2-dibutylaminoethyl) benzamide

t_R = 5.19; $(M+H)^+$ = 651.58

Example 31:

According to typical procedure B), the secondary amine **d)**, obtained via typical procedure A), is reacted with 4-n-butoxybenzoyl chloride to give



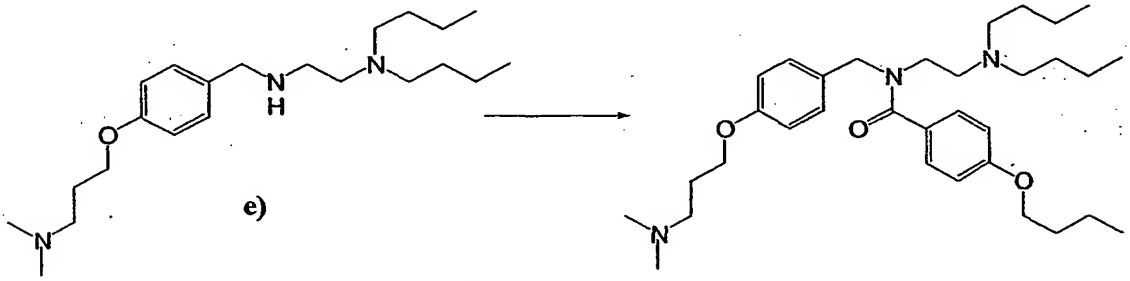
d)

N-Biphenyl-4-ylmethyl-4-butoxy-*N*-(2-dibutylaminoethyl) benzamide

t_R = 4.91; $(M+H)^+$ = 515.51

Example 32:

According to typical procedure B), the secondary amine **e)**, obtained via typical procedure A), is reacted with 4-n-butoxybenzoyl chloride to give



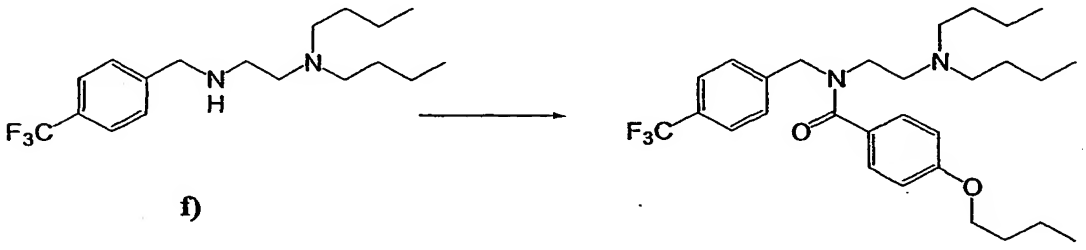
e)

4-Butoxy-*N*-(2-dibutylaminoethyl)-*N*-[4-(3-dimethylaminopropoxy) benzyl] benzamide

t_R = 3.34; $(M+H)^+$ = 540.66

Example 33:

According to typical procedure B), the secondary amine **f)**, obtained via typical procedure A), is reacted with 4-n-butoxybenzoyl chloride to give



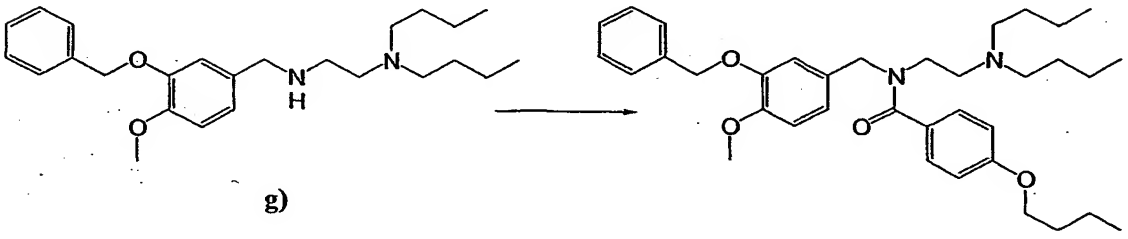
f)

4-Butoxy-*N*-(2-dibutylaminoethyl)-*N*-(4-trifluoromethyl benzyl) benzamide

t_R = 4.62; $(M+H)^+$ = 507.57

Example 34:

According to typical procedure B), the secondary amine **g)**, obtained via typical procedure A), is reacted with 4-n-butoxybenzoyl chloride to give



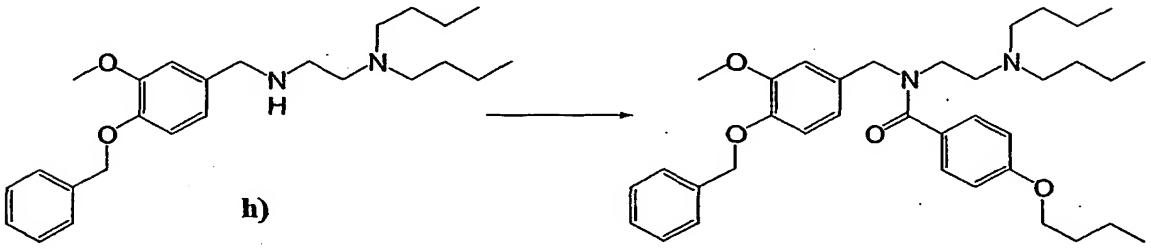
g)

N-(3-Benzyloxy-4-methoxybenzyl)-4-butoxy-*N*-(2-dibutylaminoethyl) benzamide

t_R = 4.73; $(M+H)^+$ = 575.58

Example 35:

According to typical procedure B), the secondary amine **h)**, obtained via typical procedure A), is reacted with 4-n-butoxybenzoyl chloride to give



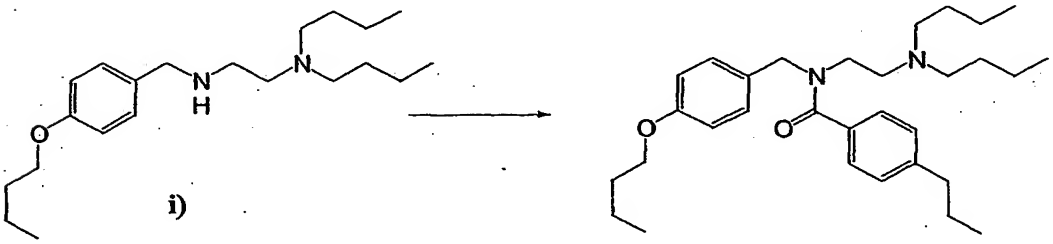
h)

N-(4-Benzyloxy-3-methoxybenzyl)-4-butoxy-*N*-(2-dibutylaminoethyl) benzamide

t_R = 4.80; $(M+H)^+$ = 575.57

Example 36:

According to typical procedure B), the secondary amine **i)**, obtained via typical procedure A), is reacted with 4-n-propylbenzoyl chloride to give



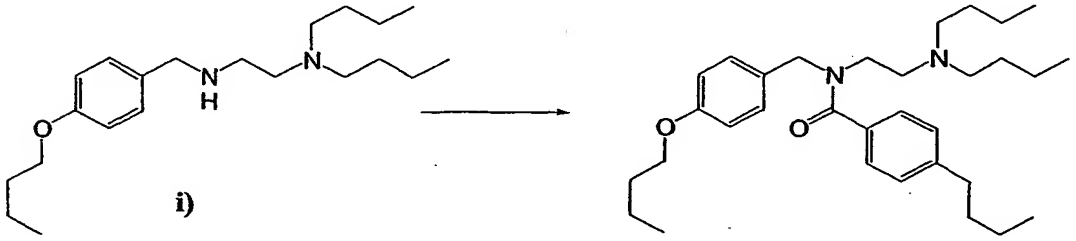
i)

N-(4-Butoxybenzyl)-*N*-(2-dibutylamino-ethyl)-4-propylbenzamide

t_R = 4.85; $(M+H)^+$ = 481.57

Example 37:

According to typical procedure B), the secondary amine **i)**, obtained via typical procedure A), is reacted with 4-n-butylbenzoyl chloride to give



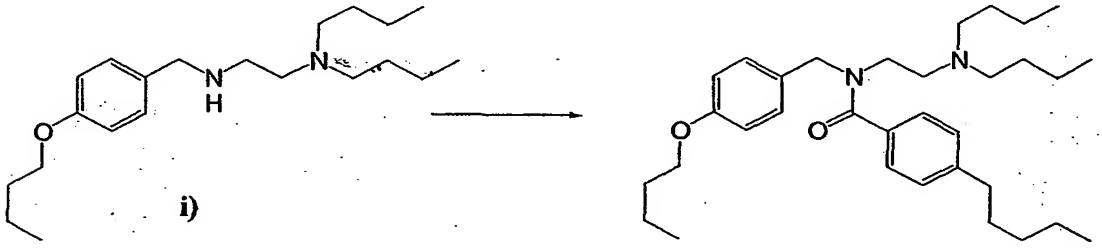
i)

N-(4-Butoxybenzyl)-4-butyl-*N*-(2-dibutylaminoethyl) benzamide

t_R = 5.02; $(M+H)^+$ = 495.51

Example 38:

According to typical procedure B), the secondary amine **i)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



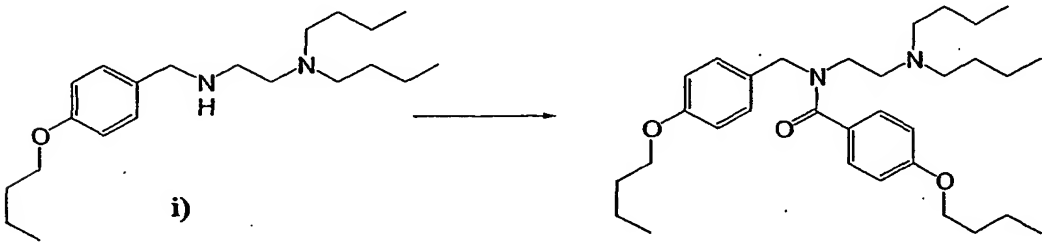
i)

N-(4-Butoxybenzyl)-*N*-(2-dibutylamino-ethyl)-4-pentylbenzamide

t_R = 5.18; $(M+H)^+$ = 509.45

Example 39:

According to typical procedure B), the secondary amine **i)**, obtained via typical procedure A), is reacted with 4-n-butoxybenzoyl chloride to give



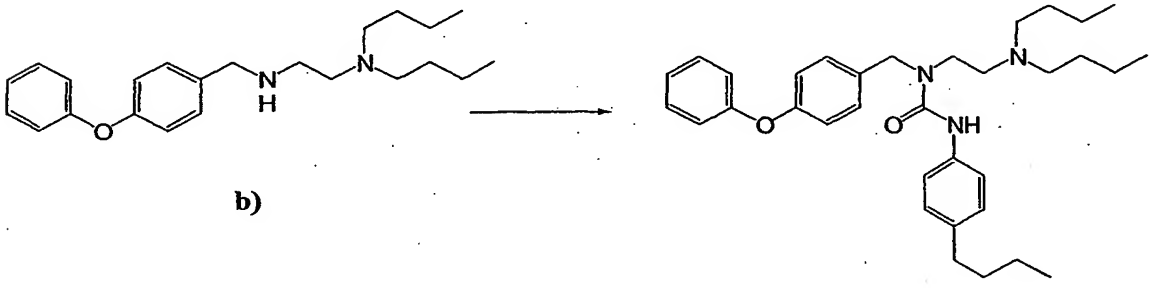
i)

4-Butoxy-*N*-(4-butoxybenzyl)-*N*-(2-dibutylaminoethyl) benzamide

t_R = 4.89; $(M+H)^+$ = 511.41

Example 40:

According to typical procedure B), the secondary amine **b)**, obtained via typical procedure A), is reacted with 4-n-butylphenylisocyanate to give



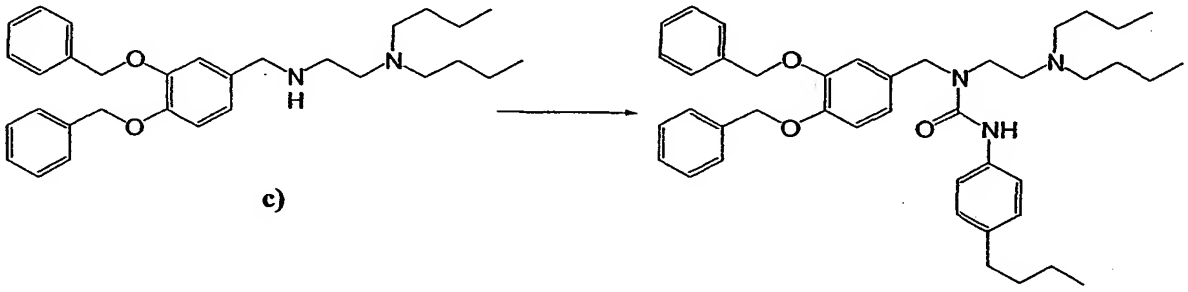
b)

3-(4-Butylphenyl)-1-(2-dibutylaminoethyl)-1-(4-phenoxybenzyl) urea

t_R = 4.98; $(M+H)^+$ = 530.53

Example 41:

According to typical procedure B), the secondary amine **c)**, obtained via typical procedure A), is reacted with 4-n-butylphenylisocyanate to give



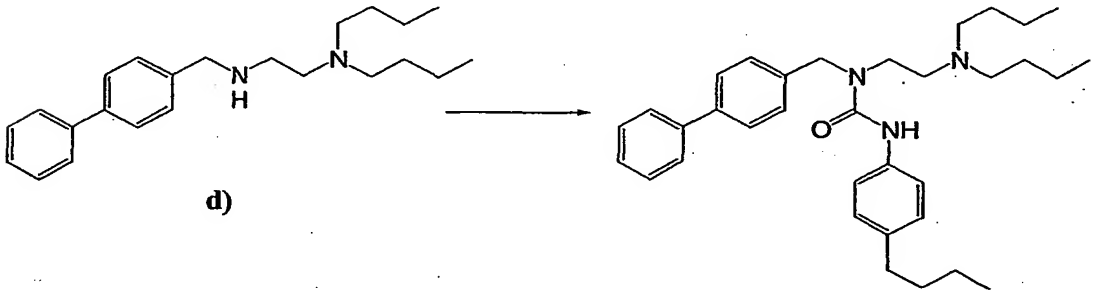
c)

1-(3,4-Bis-benzyloxybenzyl)-3-(4-butyl-phenyl)-1-(2-dibutylaminoethyl) urea

t_R = 5.24; $(M+H)^+$ = 650.63

Example 42:

According to typical procedure B), the secondary amine **d)**, obtained via typical procedure A), is reacted with 4-n-butylphenylisocyanate to give



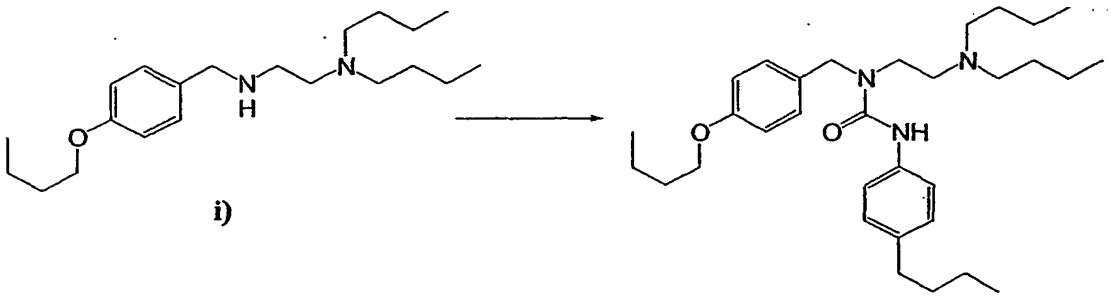
d)

1-Biphenyl-4-ylmethyl-3-(4-butylphenyl) -1-(2-dibutylaminoethyl) urea

t_R = 4.91; $(M+H)^+$ = 512.57

Example 43:

According to typical procedure B), the secondary amine **i)**, obtained via typical procedure A), is reacted with 4-n-butylphenylisocyanate to give



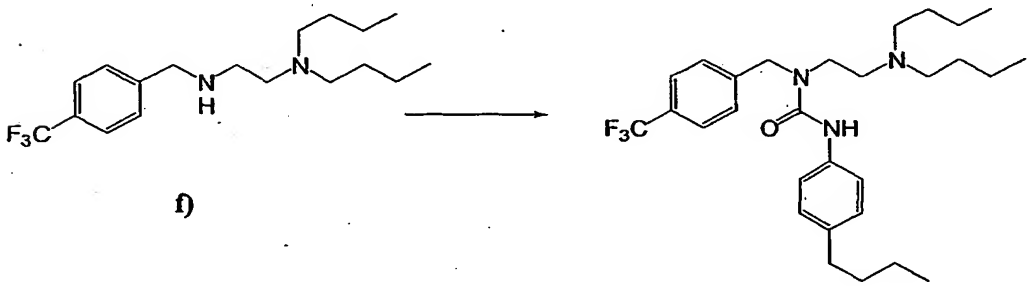
i)

1-(4-Butoxybenzyl)-3-(4-butylphenyl)-
1-(2-dibutylaminoethyl) urea

t_R = 5.08; $(M+H)^+$ = 510.65

Example 44:

According to typical procedure B), the secondary amine **f)**, obtained via typical procedure A), is reacted with 4-n-butylphenylisocyanate to give



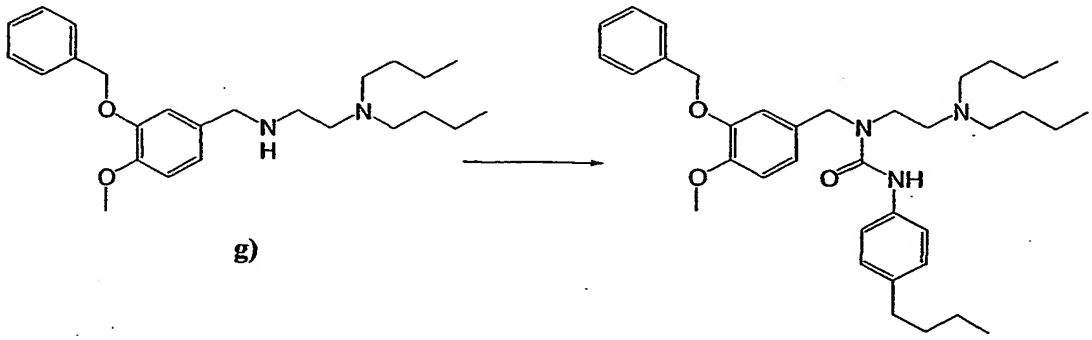
f)

3-(4-Butylphenyl)-1-(2-dibutylaminoethyl)
-1-(4-trifluoromethylbenzyl) urea

t_R = 4.86; $(M+H)^+$ =506.58

Example 45:

According to typical procedure B), the secondary amine **g)**, obtained via typical procedure A), is reacted with 4-n-butylphenylisocyanate to give



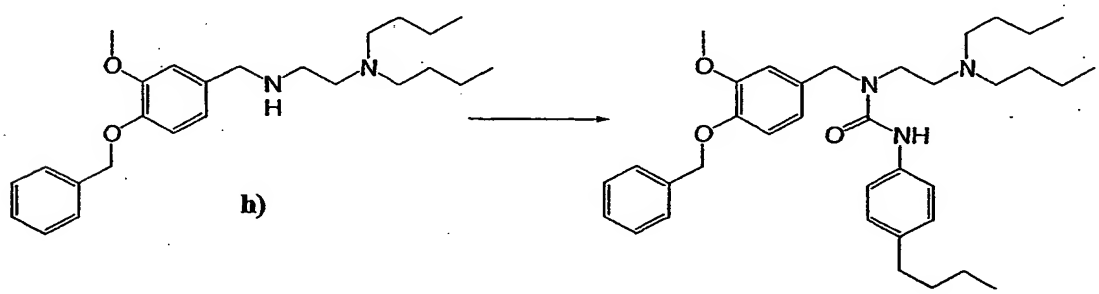
g)

1-(3-Benzyloxy-4-methoxybenzyl)-3-(4-butylphenyl)-1-(2-dibutylaminoethyl) urea

t_R = 4.82; $(M+H)^+$ = 574.56

Example 46:

According to typical procedure B), the secondary amine **h)**, obtained via typical procedure A), is reacted with 4-n-butylphenylisocyanate to give



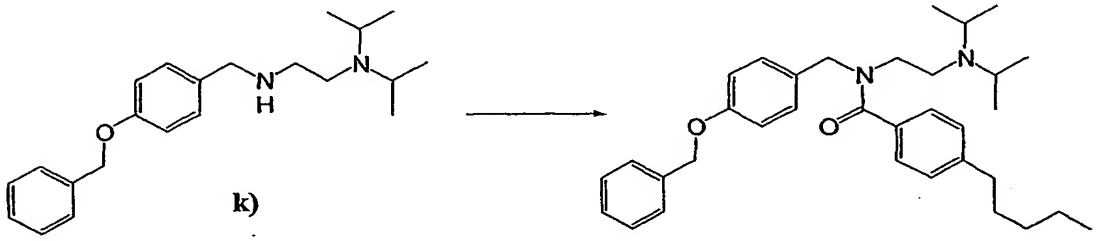
h)

1-(4-Benzyloxy-3-methoxybenzyl)-3-(4-butyl-phenyl)-1-(2-dibutylaminoethyl) urea

t_R = 4.89; $(M+H)^+$ = 574.53

Example 47:

According to typical procedure B), the secondary amine **k)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



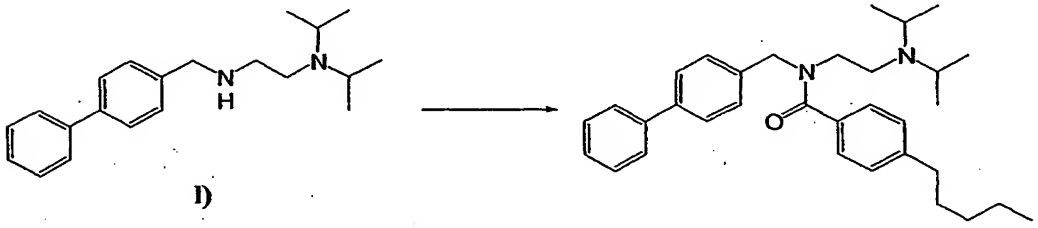
k)

N-(4-Benzyloxybenzyl)-*N*-(2-diisopropyl-aminoethyl)-4-pentylbenzamide

t_R = 4.68; $(M+H)^+$ =515.50

Example 48:

According to typical procedure B), the secondary amine **l)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



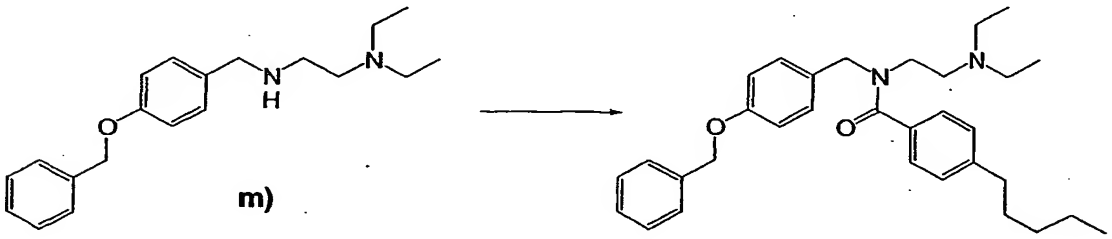
l)

N-Biphenyl-4-ylmethyl-*N*-(2-diisopropyl-aminoethyl)-4-pentylbenzamide

t_R = 4.68; $(M+H)^+$ = 485.40

Example 49:

According to typical procedure B), the secondary amine **m)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



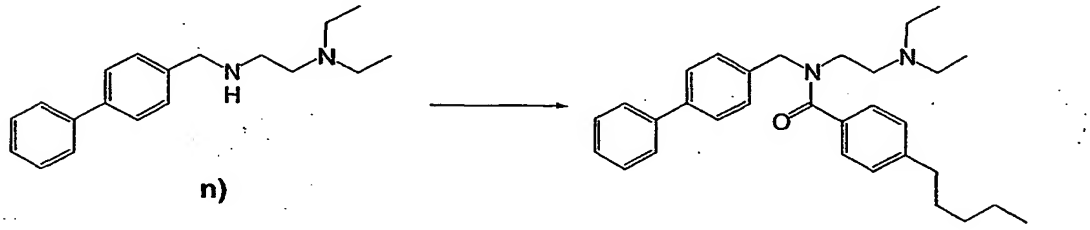
m)

N-(4-Benzyloxybenzyl)-*N*-(2-diethyl aminoethyl)-4-pentylbenzamide

t_R = 4.47; $(M+H)^+$ = 487.4

Example 50:

According to typical procedure B), the secondary amine **n)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



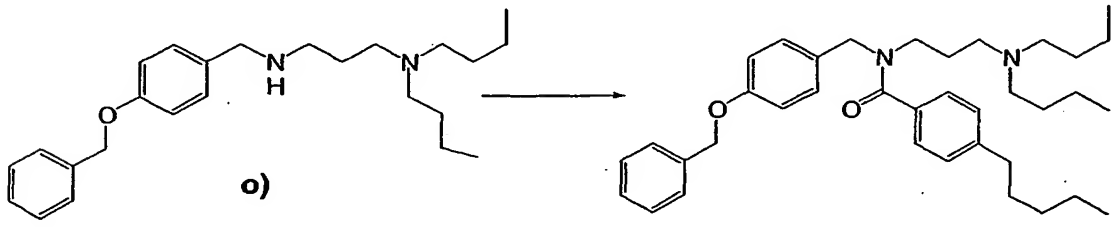
n)

N-Biphenyl-4-ylmethyl-*N*-(2-diethyl-aminoethyl)-4-pentylbenzamide

t_R = 4.47; $(M+H)^+$ = 457.40

Example 51:

According to typical procedure B), the secondary amine **o)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



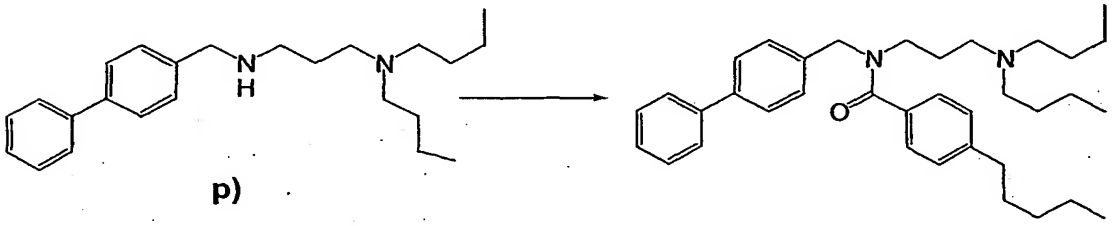
o)

N-(4-Benzyloxybenzyl)-*N*-(3-dibutyl aminopropyl)-4-pentylbenzamide

t_R = 4.94; $(M+H)^+$ = 557.50

Example 52:

According to typical procedure B), the secondary amine **p)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



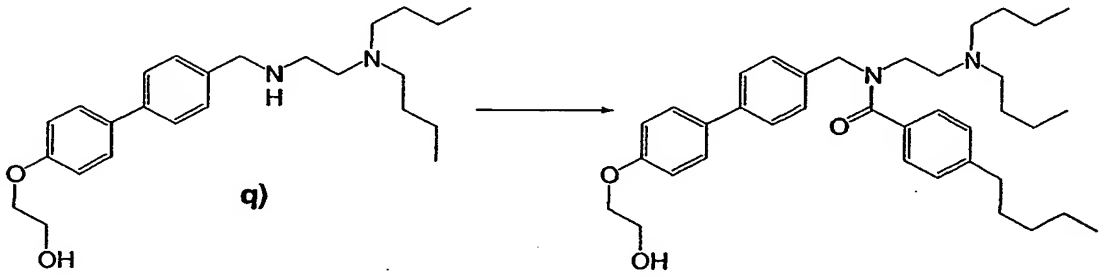
p)

N-Biphenyl-4-ylmethyl-*N*-(3-dibutyl amino propyl)-4-pentylbenzamide

t_R = 4.92; $(M+H)^+$ = 527.40

Example 53:

According to typical procedure B), the secondary amine **q)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



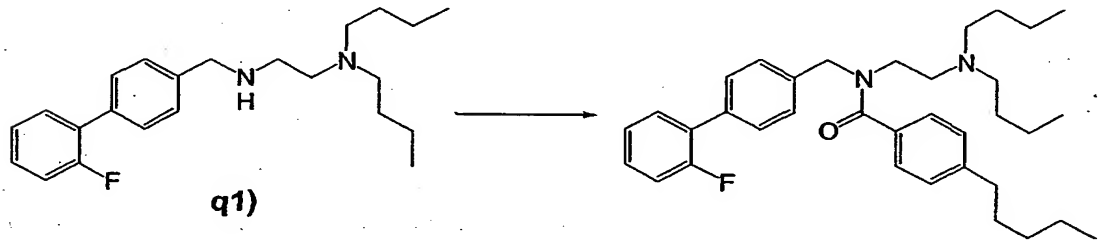
q)

N-(2-Dibutylaminoethyl)-*N*-[4'-(2-hydroxy-ethoxy) biphenyl-4-ylmethyl]-4-pentylbenzamide

t_R = 4.67; $(M+H)^+$ = 573.50

Example 54:

According to typical procedure B), the secondary amine **q1)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



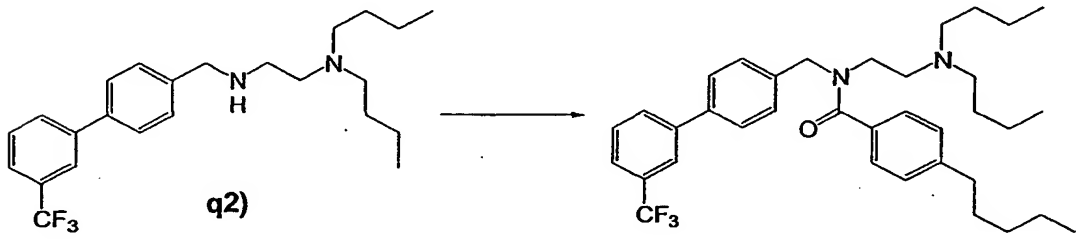
q1)

N-(2-Dibutylaminoethyl)-*N*-(2'-fluoro-biphenyl-4-ylmethyl)-4-pentylbenzamide

t_R = 5.03; $(M+H)^+$ =531.50

Example 55:

According to typical procedure B), the secondary amine **q2)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



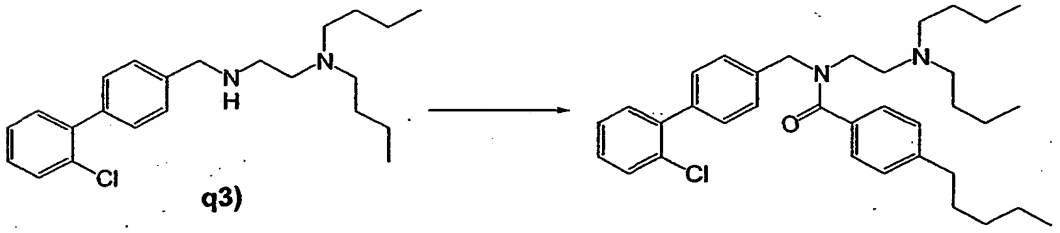
q2)

N-(2-Dibutylaminoethyl)-4-pentyl-*N*-(3'-trifluoro-methyl biphenyl-4-ylmethyl) benzamide

t_R = 5.25; $(M+H)^+$ = 581.50

Example 56:

According to typical procedure B), the secondary amine **q3)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



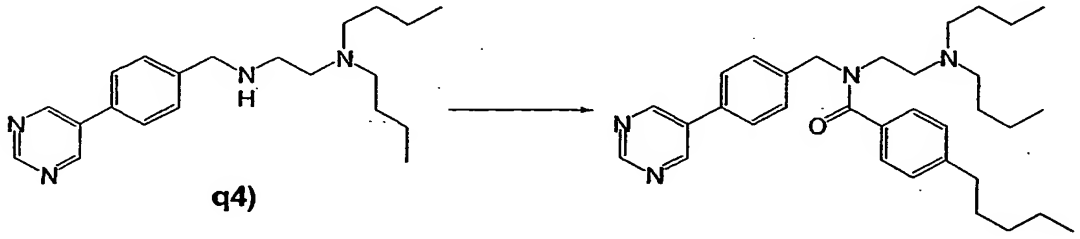
q3)

N-(2'-Chlorobiphenyl-4-ylmethyl)-*N*-(2-dibutylaminoethyl)-4-pentylbenzamide

t_R = 5.18; $(M+H)^+$ = 547.40

Example 57:

According to typical procedure B), the secondary amine **q4)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



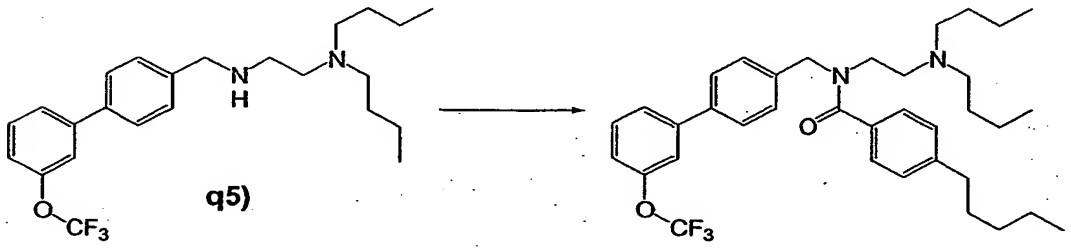
q4)

N-(2-Dibutylaminoethyl)-4-pentyl-*N*-(4-pyrimidin-5-yl-benzyl) benzamide

t_R = 4.42; $(M+H)^+$ = 515.60

Example 58:

According to typical procedure B), the secondary amine **q5)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



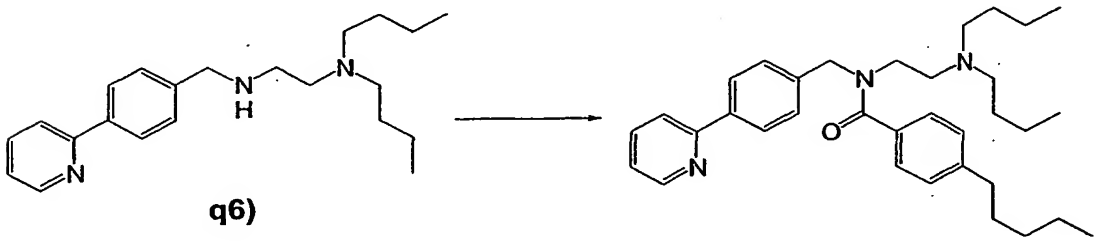
q5)

N-(2-Dibutylaminoethyl)-4-pentyl-*N*-(3'-trifluoro-methoxybiphenyl-4-ylmethyl) benzamide

t_R = 5.36; $(M+H)^+$ = 597.50

Example 59:

According to typical procedure B), the secondary amine **q6)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



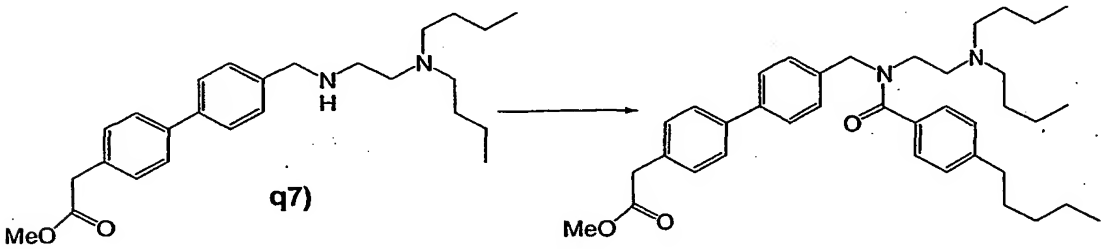
q6)

N-(2-Dibutylaminoethyl)-4-pentyl-*N*-(4-pyridin-2-yl-benzyl) benzamide

t_R = 4.60; $(M+H)^+$ = 514.50

Example 60:

According to typical procedure B), the secondary amine **q7)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



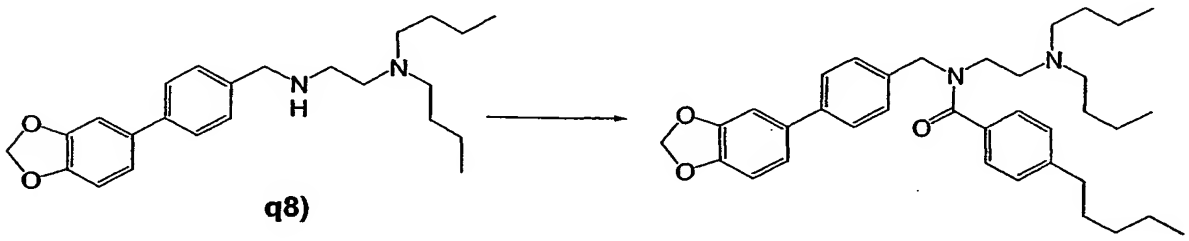
q7)

(4'-{[(2-Dibutylaminoethyl)-(4-pentylbenzoyl)amino]methyl} biphenyl-4-yl) acetic acid methyl ester

t_R = 5.03; $(M+H)^+$ = 585.64

Example 61:

According to typical procedure B), the secondary amine **q8)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



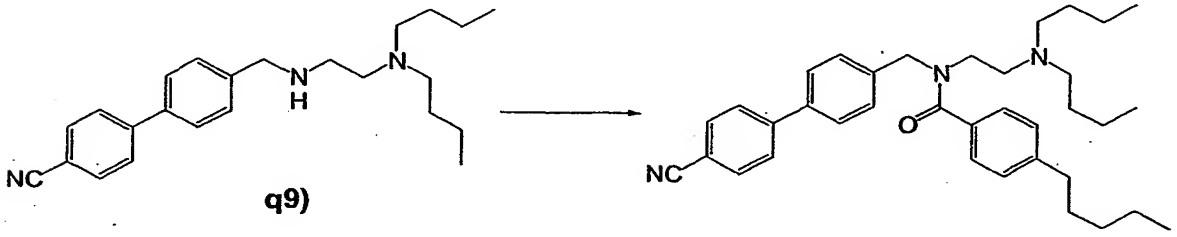
q8)

N-(4-Benzo[1,3]dioxol-5-yl-benzyl)-*N*-(2-dibutyl-aminoethyl)-4-pentylbenzamide

t_R = 5.18; $(M+H)^+$ = 557.51

Example 62:

According to typical procedure B), the secondary amine **q9)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



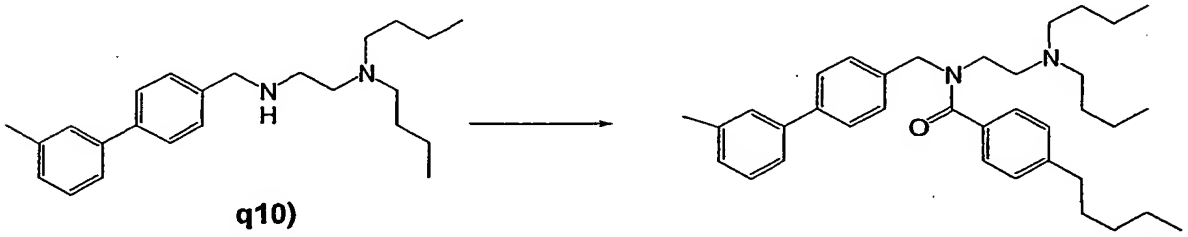
q9)

N-(4'-Cyanobiphenyl-4-ylmethyl)-*N*-(2-dibutyl-aminoethyl)-4-pentylbenzamide

t_R = 5.11; $(M+H)^+$ = 538.40

Example 63:

According to typical procedure B), the secondary amine **q10)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



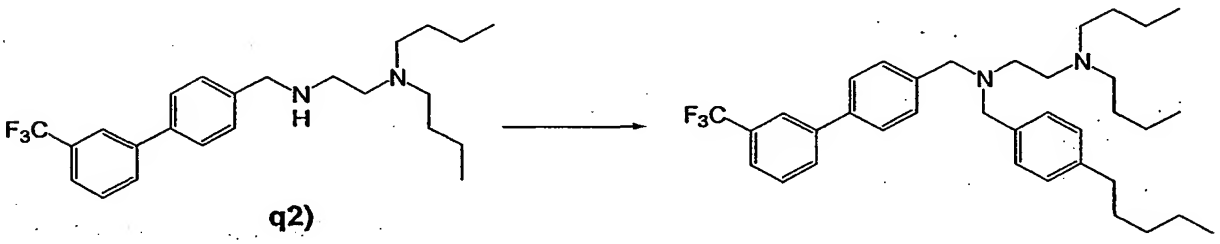
q10)

N-(2-Dibutylaminoethyl)-*N*-(3'-methylbiphenyl-4-ylmethyl)-4-pentylbenzamide

t_R = 5.52; $(M+H)^+$ = 527.42

Example 64:

According to typical procedure C), the secondary amine **q2)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzaldehyde to give



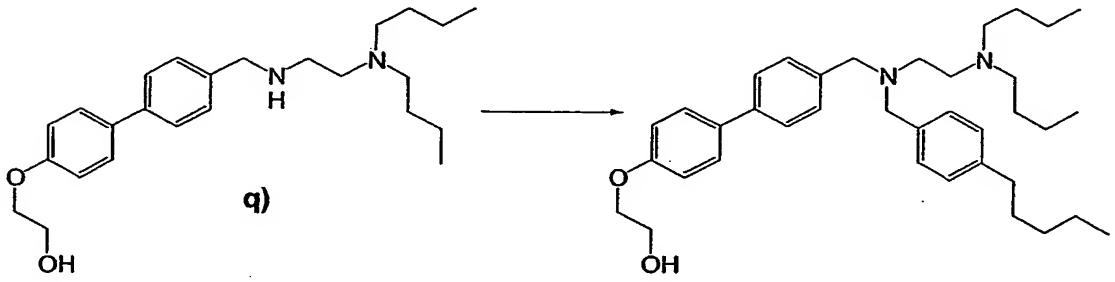
q2)

N,*N*-Dibutyl-*N'*-(4-pentylbenzyl)-*N'*-(3'-trifluoromethylbiphenyl-4-ylmethyl)ethane-1,2-diamine

t_R = 5.73; $(M+H)^+$ = 567.51

Example 65:

According to typical procedure C), the secondary amine **q)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzaldehyde to give



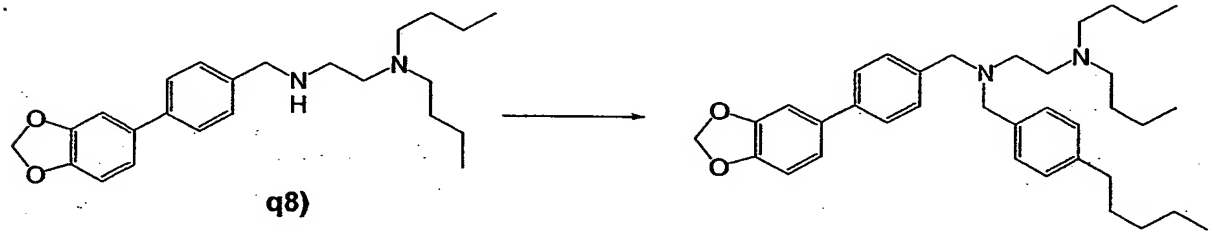
q)

2-(4'-{[(2-Dibutylaminoethyl)(4-pentylbenzyl) amino]methyl}biphenyl-4-yloxy) ethanol

t_R = 5.06; $(M+H)^+$ = 559.50

Example 66:

According to typical procedure C), the secondary amine **q8)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzaldehyde to give



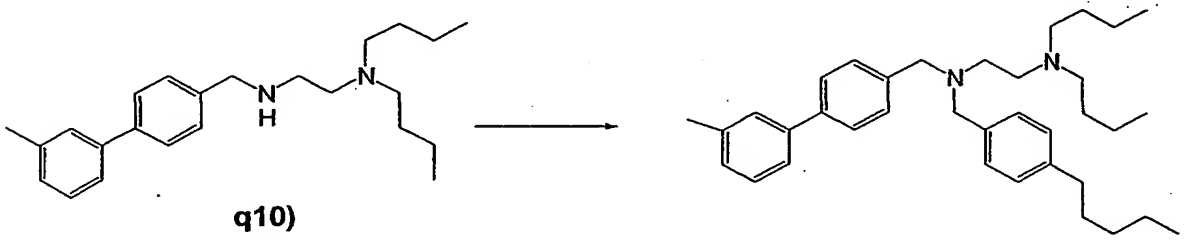
q8)

N-(4-Benzo[1,3]dioxol-5-yl-benzyl)-*N'*,*N'*-dibutyl-*N*-(4-pentylbenzyl)ethane-1,2-diamine

t_R = 5.47; $(M+H)^+$ = 543.38

Example 67:

According to typical procedure C), the secondary amine **q10)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzaldehyde to give



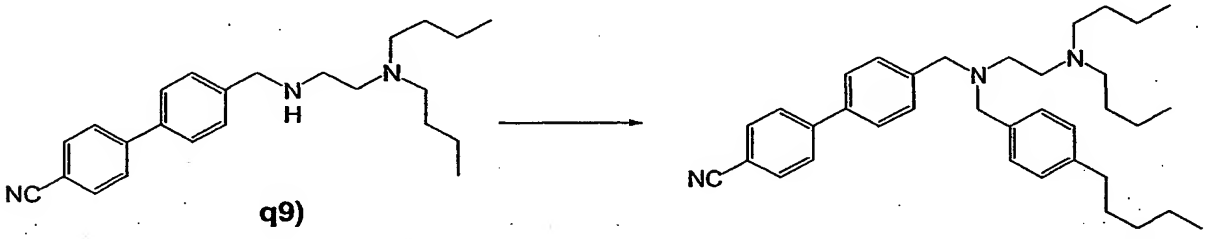
q10)

N,*N*-Dibutyl-*N'*-(3'-methylbiphenyl-4-ylmethyl)-*N'*-(4-pentylbenzyl)ethane-1,2-diamine

t_R = 5.51; $(M+H)^+$ = 513.69

Example 68:

According to typical procedure C), the secondary amine **q9)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzaldehyde to give



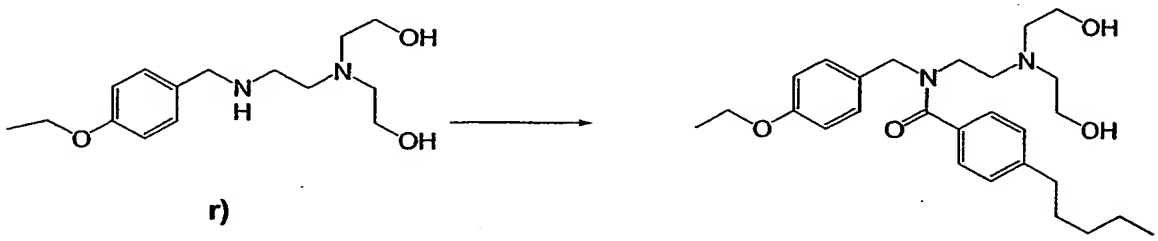
q9)

4'-{[(2-Dibutylaminoethyl)-(4-pentylbenzyl)amino]-methyl}biphenyl-4-carbonitrile

t_R = 5.34; $(M+H)^+$ = 524.40

Example 69:

According to typical procedure B), the secondary amine **r)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



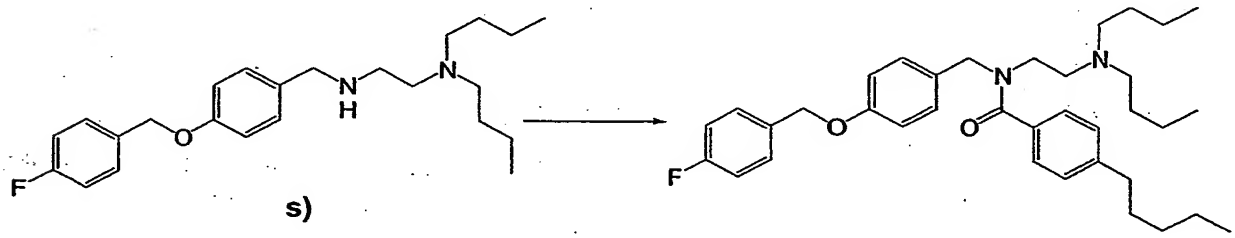
r)

N-{2-[Bis-(2-hydroxyethyl)amino]ethyl}-*N*-(4-ethoxybenzyl)-4-pentylbenzamide

t_R = 4.17; $(M+H)^+$ = 457.47

Example 70:

According to typical procedure B), the secondary amine **s)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



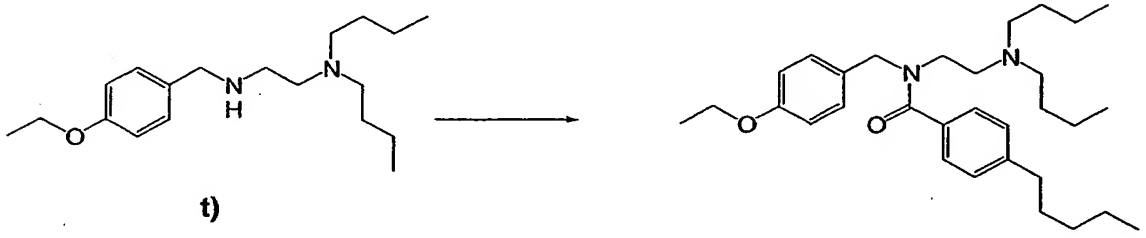
s)

N-(2-Dibutylaminoethyl)-*N*-[4-(4-fluorobenzyloxy) benzyl]-4-pentylbenzamide

t_R = 5.29; $(M+H)^+$ = 561.54

Example 71:

According to typical procedure B), the secondary amine **t)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



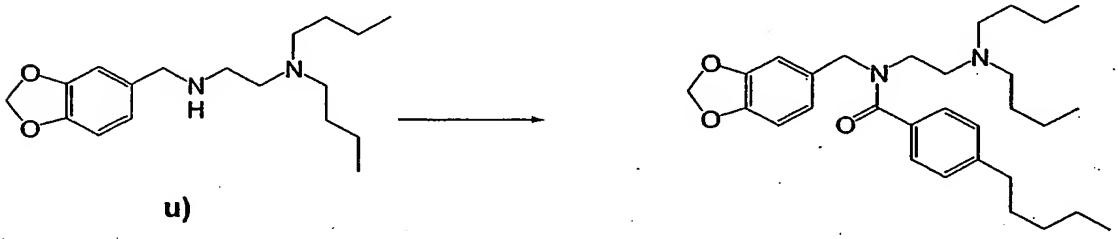
t)

N-(2-Dibutylaminoethyl)-*N*-(4-ethoxybenzyl)-4-pentylbenzamide

t_R = 4.98; $(M+H)^+$ = 481.45

Example 72:

According to typical procedure B), the secondary amine **u)**, obtained via typical procedure A), is reacted with 4-n-pentylbenzoyl chloride to give



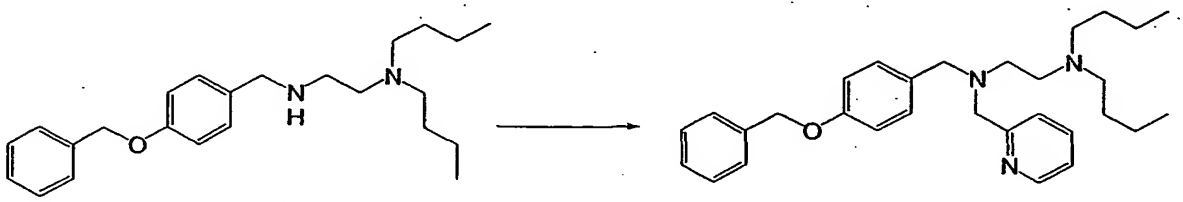
u)

N-Benzo[1,3]dioxol-5-ylmethyl-*N*-(2-dibutyl-aminoethyl)-4-pentylbenzamide

t_R = 4.55; $(M+H)^+$ = 481.61

Example 73:

According to typical procedure C), the secondary amine **a)**, obtained via typical procedure A), is reacted with pyridine-2-carbaldehyde to give



a)

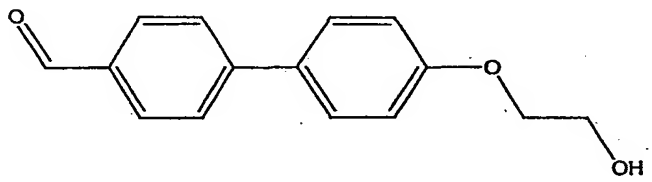
N-(4-Benzyloxybenzyl)-*N'*,*N'*-dibutyl-*N*-pyridin-2-ylmethylethane-1,2-diamine

t_R = 4.17; $(M+H)^+$ = 460.27

c) Referential Examples:

Referential Example 1:

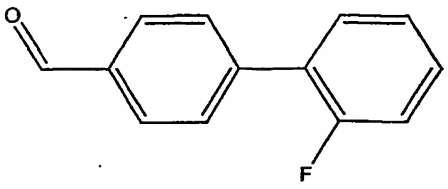
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 2-(4-bromophenoxy) ethanol to give



4'-(2-Hydroxyethoxy)biphenyl-4-carbaldehyde

Referential Example 2:

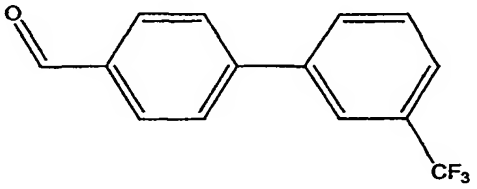
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-2-fluorobenzene to give



2'-Fluorobiphenyl-4-carbaldehyde

Referential Example 3:

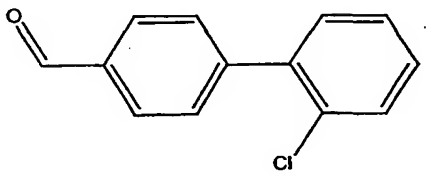
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 3-bromobenzotrifluoride to give



3'-Trifluoromethylbiphenyl-4-carbaldehyde

Referential Example 4:

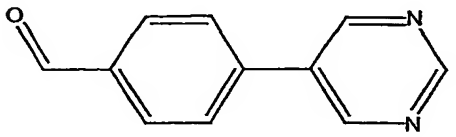
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-2-chlorobenzene to give



2'-Chlorobiphenyl-4-carbaldehyde

Referential Example 5:

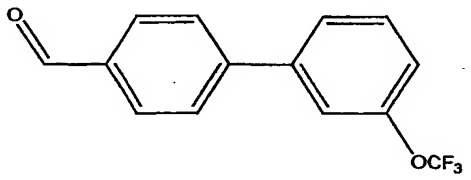
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 5-bromopyrimidine to give



4-Pyrimidin-5-yl-benzaldehyde

Referential Example 6:

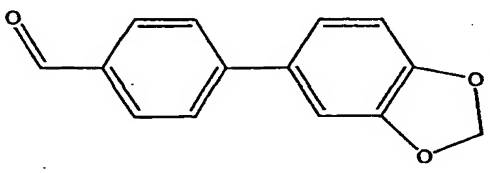
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-3-(trifluoromethoxy)benzene to give



3'-Trifluoromethoxybiphenyl-4-carbaldehyde

Referential Example 7:

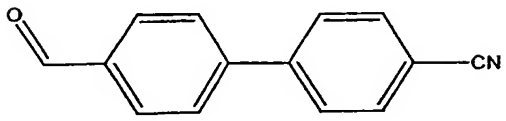
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 5-bromobenzo[1,3]dioxole to give



4-Benzo[1,3]dioxol-5-yl-benzaldehyde

Referential Example 8:

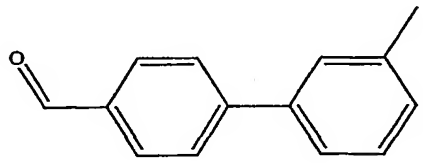
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 4-bromobenzonitrile to give



4'-Formyl-biphenyl-4-carbonitrile

Referential Example 9:

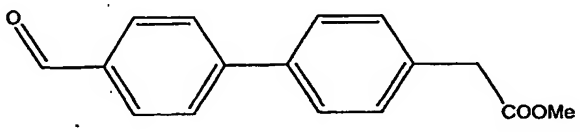
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 3-bromotoluene to give



3'-Methyl-biphenyl-4-carbaldehyde

Referential Example 10:

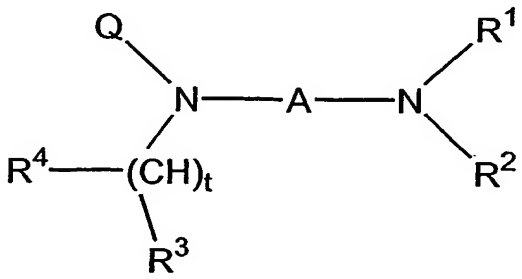
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 4-bromophenyl acetic acid methyl ester to give



(4'-Formylbiphenyl-4-yl) acetic acid methyl ester

Claims:

1. Compounds of the **general formula I**



General Formula I

wherein

Q represents $-SO_2-R^5$; $-CO-R^5$; $-CO-NH-R^5$; $-CO-N(R^5)(R^6)$; $-CO-OR^5$; $-(CH_2)_p-R^5$; $-(CH_2)_p-CH(R^5)(R^6)$;

R^1 and R^2 represent propyl; butyl; pentyl; hexyl; ω-hydroxy-propyl; ω -hydroxy-butyl; ω-hydroxy-pentyl; ω-hydroxy-hexyl; lower alkoxy-propyl; lower alkoxy-butyl; lower alkoxy-pentyl; lower alkoxy-hexyl; aryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; heterocyclyl; and can be the same or different; or R^1 and R^2 and the nitrogen atom together can represent a ring such as azetidin; azepan;

R^3 represents lower alkyl; lower alkenyl; aryl; heteroaryl; cycloalkyl; heterocyclyl; aryl-lower alkyl; heteroaryl-lower alkyl; cycloalkyl-lower alkyl; heterocyclyl-lower alkyl; aryl-lower alkenyl; heteroaryl-lower alkenyl; cycloalkyl-lower alkenyl; heterocyclyl-lower alkenyl;

R^4 represents hydrogen; $-CH_2-OR^7$; $-CO-OR^7$; lower alkyl;

R^5 and R^6 represent lower alkyl; lower alkenyl; aryl; heteroaryl; cycloalkyl; heterocyclyl; aryl-lower alkyl; heteroaryl-lower alkyl; cycloalkyl-lower alkyl;

heterocyclyl-lower alkyl; aryl-lower alkenyl; heteroaryl-lower alkenyl; cycloalkyl-lower alkenyl; heterocyclyl-lower alkenyl;

R^7 represents hydrogen, lower alkyl; cycloalkyl; aryl; cycloalkyl-lower alkyl; aryl-lower alkyl;

t represents the whole numbers 0 (zero) or 1 and in case t represents the whole number 0 (zero), R^4 is absent;

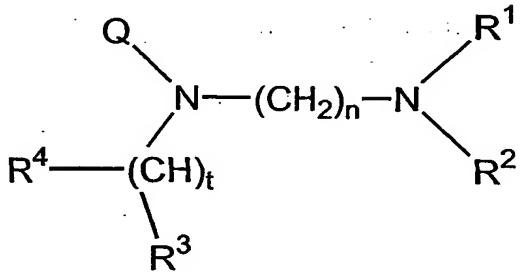
p represents the whole numbers 0 (zero), 1 or 2;

A represents $-(CH_2)_n-$;

n represents the whole numbers 2, 3, 4 or 5;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof

2. Compounds of **formula II**



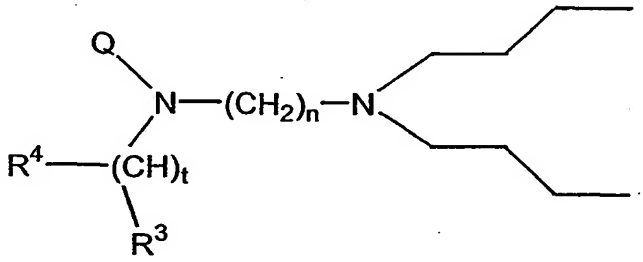
Formula II

wherein

Q, **t**, R^3 and R^4 are as defined in general formula I above, R^1 and R^2 represent lower alkyl and **n** represents the whole numbers 2 or 3

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

3. Compounds of **formula III**



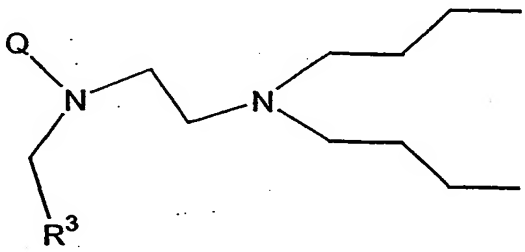
Formula III

wherein

Q, **t**, R^3 and R^4 are as defined in general formula I above and **n** represents the whole numbers 2 or 3

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

4. Compounds of **formula IV**



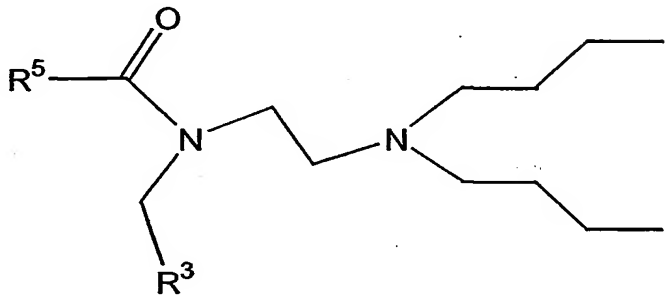
Formula IV

wherein

Q and R^3 are as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

5. Compounds of **formula V**

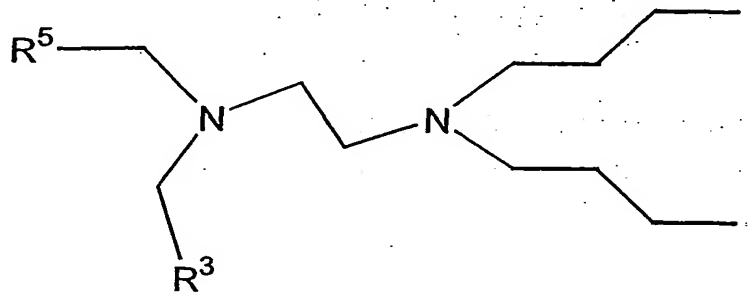


Formula V

wherein R^3 and R^5 are as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

6. Compounds of **formula VI**



Formula VI

wherein R^3 and R^5 are as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

7. The compounds according to any one of claims 1 - 6

N-(4-Benzyloxybenzyl)-N-(2-dibutylamino-ethyl)-4-pentylbenzamide;
N-Biphenyl-4-ylmethyl-N-(2-dibutylamino-ethyl)-4-pentylbenzamide;
N-(2-Dibutylaminoethyl)-N-[4'-(2-hydroxy-ethoxy)-biphenyl-4-ylmethyl]-4-pentylbenzamide;

N-(4-Benzo[1,3]dioxol-5-yl-benzyl)-N-(2-dibutyl-aminoethyl)-4-pentylbenzamide.

8. Pharmaceutical compositions containing one or more compounds as claimed in any one of claims 1 to 7 and inert excipients.

9. Pharmaceutical compositions according to claim 8 for treatment of diseases demanding the inhibition of aspartic proteases.

10. Pharmaceutical compositions according to claim 8 for treatment of disorders associated with the role of plasmepsin II and which require selective inhibition of plasmepsin II.

11. Pharmaceutical compositions according to claim 8 for treatment or prevention of malaria.

12. Pharmaceutical compositions according to claim 8, which contain aside of one or more compounds of the general formula I a known inhibitor of plasmepsin II, HIV protease or cathepsin D or E.

13. A process for the preparation of a pharmaceutical composition according to any one of claims 9 to 12, characterized by mixing one or more active ingredients according to any one of claims 1 to 7 with inert excipients in a manner known per se.

14. Use of at least one of the compounds of the general formula I for the treatment or prevention of diseases.

15. The novel compounds, processes and methods as well as the use of such compounds substantially as described herein before.

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International Bureau

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PCT

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WO 02/038534 A3

(54) Title: SUBSTITUTED ALKYLDIAMINES AS INHIBITORS OF PLASMEPSIN OR RELATED PROTEASES

(57) Abstract: The invention relates to novel compounds which are substituted alkyldiamino derivatives of formula (I). The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I) and especially their use as inhibitors of the plasmodium falciparum protease plasmepsin II or related aspartic proteases.

INTERNATIONAL SEARCH REPORT

In...ional Application No
PCT/EP 01/12617

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/78 C07C275/32 C07C217/58 C07D239/26 C07D213/38
C07D317/58 A61K31/36 A61K31/44 A61K31/165 A61K31/17
A61P33/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 27 10 047 A (LABAZ) 15 September 1977 (1977-09-15) page 6 e.g. compounds 1,9,11,14 page 16 ---	1-3,8, 13,14
X	GOLDENBERG, CHARLES ET AL: "Benzofurans. LX. Potential antianginal sulfonylaminobenzoylbenzofurans" EUR. J. MED. CHEM. - CHIM. THER., vol. 12, no. 1, 1977, pages 81-86, XP001064371 page 85 --- -/--	1-3,8, 13,14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2002	28. 06. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bader, K

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INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 01/12617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GRISAR, J. MARTIN ET AL: "Bis basic-substituted polycyclic aromatic compounds. New class of antiviral agents. 4. Bis basic sulfonamides of anthraquinone" J. MED. CHEM., vol. 17, no. 8, 1974, pages 890-893, XP000608424 page 892; table II ---	1-3,8, 13,14
X	PATENT ABSTRACTS OF JAPAN vol. 011, no. 317 (C-452), 15 October 1987 (1987-10-15) & JP 62 103066 A (ASAHI CHEM IND CO LTD;OTHERS: 01), 13 May 1987 (1987-05-13) abstract ---	1-3,8, 13,14
X,P	HARMSE, L. ET AL: "Structure-activity relationships and inhibitory effects of various purine derivatives on the in vitro growth of Plasmodium falciparum" BIOCHEMICAL PHARMACOLOGY, vol. 62, no. 3, 2001, pages 341-348, XP001066310 compound 40 and also under 3.7 "A ntimalarial activity of compound 40" page 346; figure 4 ---	1,2,8-15
X,P	CAULFIELD, WILSON L. ET AL: "The first potent and selective inhibitors of the glycine transporter type 2" JOURNAL OF MEDICINAL CHEMISTRY, vol. 44, no. 17, 2001, pages 2679-2682, XP002183670 page 2681; table 1 ---	1,2,8-15
A	ELSLAGER, EDWARD F. ET AL: "Antimalarial drugs. 35. Synthesis and antimalarial effects of 1-(3,4-dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine and related substances" J. MED. CHEM., vol. 17, no. 1, 1974, pages 75-100, XP002933212 page 78; table 1 -----	1,8,11, 14,15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 01/12617

Box I Observations where certain claims were found unsearchable (C ntinuati n of it m 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14 and 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

,8-15 (all partially)

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-4,8-15 (all partially)

   Compounds according to claim 1 wherein Q= -SO2-R5

2. Claims: 1-5,8-15 (all partially); 7 (completely)

   Compounds according to claim 1 wherein Q = -CO-R5.

3. Claims: 1-4,8-15 (all partially)

   Compounds according to claim 1 wherein Q = -CO-NH-R5 or Q = -CO-N(R5)(R6).

4. Claims: 1-4,8-15 (all partially)

   Compounds according to claim 1 wherein Q= -CO-OR5.

5. Claims: 1-4,8-15 (all partially); 6 (completely)

   Compounds according to claim 1 wherein Q = -(CH2)p-R5 or Q = -(CH2)p-CH(R5)(R6).

INTERNATIONAL SEARCH REPORT

Information on patent family members

In...tional Application No
PCT/EP 01/12617

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		JP 6002741 B	12-01-1994